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Cancer and Fever

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Synonym

Fever in cancer; Neoplastic fever

Definition

A significant fever in patients with cancer is always a serious concern. Though it usually indicates the presence of an infection, a source is sometimes difficult to detect – and is not always found – even after an extensive investigation. This often leaves the caring physician perplexed and concerned. As cancer patients undergo several types of treatments such as antineoplastic chemotherapy, immunotherapy, targeted therapy, radiation therapy, surgery, and blood transfusions, the differential diagnosis for fever can become more complicated and requires a carefully measured evaluation. Among the variety of causes of fever, one of not uncommon etiology is fever of paraneoplastic manifestation, which is a febrile condition occurring as a result of the biologic effects from cancer itself.

Fever that occurs as a paraneoplastic manifestation is seen frequently in Hodgkin's disease and non-Hodgkin lymphomas, acute and chronic leukemias, multiple myeloma, and other solid tumors such as renal cell cancer. This paraneoplastic fever, which is defined as fever caused by cancer itself, has been shown to be the cause of fever of unknown origin (FUO) in approximately 20 % of cases as shown in Table 1 (Jacoby and Swartz 1973; Vanderschueren et al. 2003).

In this entry, several aspects of paraneoplastic fever will be discussed. The aim is to examine the differential diagnosis for various causes of fever with particular emphasis on diagnostic approaches. In addition, clinical characteristics, possible pathogenesis, and management of paraneoplastic fever will be evaluated.

Pathophysiology of Fever

"Pyrogen" is termed to describe any substance that produces fever. The pathogenesis of fever in man begins with the production of endogenous pyrogens by phagocytic leukocytes in response to exogenous pyrogens (i.e., toxins from bacteria, fungi, and yeasts, including endotoxins, exotoxins, and enterotoxins, as well as drugs such as bleomycin and cisplatin). Endogenous pyrogens, which are now known as pyrogenic cytokines, are produced as the result of an infectious as well as inflammatory process in the body. These pyrogenic cytokines are specific cytokines produced upon activation of toll-like

Cancer and Fever, Table 1 Classic causes of fever of unknown origin (FUO) in the general population (Jacoby and Swartz 1973; Vanderschueren et al. 2003)

Category	Percentage of FUO population (%)	Common
Infectious diseases	30–40 %	Tuberculosis, abscesses, osteomyelitis, endocarditis, cytomegalovirus, cat scratch disease
Connective tissue disease	20–30 %	Adult Still's disease, polymyalgia rheumatica, giant cell arteritis, polyarteritis nodosa, systemic lupus erythematosus, late-onset rheumatoid arthritis
Neoplastic disorders	20–30 %	Lymphoma, leukemia, renal cell carcinoma, hepatocellular carcinoma or other tumors metastatic to the liver, primary or metastatic central nervous system tumors
Miscellaneous disorders	15–20 %	Drug fever, alcoholic cirrhosis, Crohn's disease, subacute thyroiditis, factitious fever

receptor (TLR) (Mackowiak et al. 1992), and further regulate immune, inflammatory, and hematopoietic processes.

There are several well-known pyrogenic cytokines which include interleukin (IL)-1, IL-6, tumor necrosis factor (TNF), ciliary neurotrophic factor (CNTF), and interferon-α (IFN-α) (Dinarello 1999; Shapiro et al. 1993). Fever is produced by an interaction between pyrogenic cytokines and specialized receptors on or near thermosensitive neurons in the thermoregulatory center of the anterior hypothalamus. This interaction may cause local hypothalamic production and release of prostaglandins, monoamines, and, possibly cyclic AMP, which are all thought to have a role in fever. From the anterior hypothalamus, information is transmitted through the posterior hypothalamus to the vasomotor center, which directs sympathetic-nerve fibers to constrict peripheral vessels and decrease heat dissipation (Dinarello and Wolf 1978). Some data has suggested that although up to 70 % of patients with cancer have fever, it is more often infection or localized obstruction caused by the tumor that is responsible for the fever in the majority of the cases (Browder et al. 1961).

The pathophysiology of paraneoplastic fever in patients without overt infection or obstruction is still uncertain. However, the mechanism for paraneoplastic fever does seem to be distinct from that for fever due to infection. Research has suggested the involvement of various cytokines. Indeed, cancer cells and the immune system appear to overexpress a range of cytokines such as IL-1, TNF, IL-2, IL-6, IL-12, and interferon in patients with malignancies.

Under normal circumstances, the hematopoietic and immune systems do not produce many of the known cytokines at significant levels. However, cancer cells may produce high levels of cytokines, such as IL-1 or IL-6. Patients with lymphoma have high levels of IL-6 and IL-10. Additionally serum levels of IL-6 have correlated with the presence of B-symptoms in diffuse large cell lymphoma (Seymour et al. 1995). In patients with renal cell carcinomas, increased IL-6 levels have been associated with an increased incidence of paraneoplastic fever as well as shorter survival (Blay et al. 1992; Blay et al. 1997; Kurzrock 2001).

These cytokines can go on to act as autocrine growth factors that stimulate tumor growth and also induce production of other cytokines through the immune system. It is one of the axioms of cytokine research that virtually every cytokine induces many other cytokines and a "snowball" effect occurs once these pathways are deregulated (Kurzrock 2001).

Another mechanism for paraneoplastic fever may be related to inflammation due to tumor necrosis, which some investigators have attributed to the release of TNF and other endogenous pyrogens from dead tissue (Johnson 1996). For example, bone marrow necrosis is due to malignancy in the vast majority of cases, and fever has been documented in 68 % cases of bone marrow

necrosis. Bone marrow necrosis may also cause the release of toxins and cytokines from damaged cells (Janssens et al. 2000).

Infectious fever is produced by a combination of exogenous and endogenous pyrogens that are responsible for prostaglandin-mediated activation of thermoregulatory neurons of the anterior hypothalamic area while paraneoplastic fever is most likely primarily mediated by IL-6 and TNF, which have direct effects to thermoregulatory neurons to elevate body temperature. These differences in pathophysiology may explain not only the different clinical features between fever of infection and fever from malignancy but also the distinctly different response of the two conditions to the naproxen test.

Cancer and Fever, Table 2 Causes of fever in patients with cancer

Causes	Examples
Neoplastic origin	Hodgkin and non-Hodgkin lymphomas, acute and chronic leukemias, multiple myeloma, solid tumors such as renal cell cancer
Infections	Bacterial, fungal, viral, and/or parasitic
Drug reaction	Amphotericin B
Chemotherapy-related	Asparaginase, bleomycin, interferons
Central nervous system metastasis	Hypothalamic involvement, meningeal carcinomatosis
Radiation-induced	Radiation pneumonitis
Endocrine disorder	Steroid-induced adrenal insufficiency or crisis
Blood transfusion reaction	

Fever in Cancer

Fever, whether it presents with or without infection, requires immediate attention in cancer patients because delayed diagnosis and treatment will result in significant morbidity and mortality. Early recognition of a life-threatening infection such as pneumonia or sepsis is crucial. Additionally, the understanding of the cause of a fever and its clinical manifestations will provide timely evaluation and treatment, as well as reduce patient discomfort and unnecessary expenses. The various conditions that can cause fever in patients with cancer are summarized in Table 2.

Neutropenic Fever

In patients with cancer, especially in an immunocompromised and marrow-suppressed state, the most common cause of fever is infection. Infections may be of bacterial, viral, fungal, or parasitic origin. Fever can sometimes be the only manifestation of infection in cancer patients, particularly in those who are neutropenic, because signs and symptoms of inflammation are typically attenuated.

Fever occurs frequently during chemotherapy-induced neutropenia: 10–50 % of patients with solid tumors and >80 % of those with hematologic malignancies will develop fever during one more cycles of chemotherapy associated with neutropenia (Klastersky 2004). For most of these patients, no infectious etiology is documented. Clinically documented infections occur in 20–30 % of febrile episodes, with the intestinal tract, lung, and skin being common sites of tissue-based infection (Freifeld et al. 2011).

Most experts consider high-risk patients to be those with anticipated prolonged (>7 days duration) and profound neutropenia (absolute neutrophil count $\leq$100 cells/mm^3 following cytotoxic chemotherapy) and/or significant medical comorbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes (Freifeld et al. 2011). During the initial assessment, a detailed history should include elicitation of new site-specific symptoms, infection exposures, and prior documented infections. Physical examination of febrile neutropenic patients requires a thorough search to detect subtle signs and symptoms. Close attention to sites which are most commonly infected is warranted. These sites include skin (including sites of procedures or central lines), oropharynx, lungs, and perineum. Laboratory tests should include a complete blood count (CBC) with differential, comprehensive metabolic panel, and at least two sets of blood cultures. In addition,

if clinically indicated, experts also recommend culture specimens from other sites of infection and a chest X-ray.

Patients with cancer and febrile neutropenia after require hospitalization for empiric IV antibiotic therapy. Monotherapy with an anti-pseudomonal B-lactam agent, such as cefepime, is initially recommended. Other antimicrobials may be added to the regimen for management of complications or if antimicrobial resistance is suspected or documented.

Drug Reaction

Another common cause of fever in cancer patients is fever caused by a reaction to drugs. Drugs utilized in the care of patients with cancer fall into two major categories – those used for supportive care and those given to treat the cancer itself (i.e., chemotherapy).

Drugs that are known to cause fever include growth factors such as filgrastim and sargramostim. Allopurinol is an uncommon but important cause of drug fever, as it is frequently used in patients with leukemia and lymphoma to prevent or diminish tumor lysis syndrome. Allopurinol-induced drug fever is often accompanied by hepatotoxicity, deterioration of renal function, severe rash, and eosinophilia (Arellano and Sacristan 1993). Amphotericin B, a parenteral agent often used in cancer patients for broad antifungal coverage, is commonly known to cause fevers, chills, and malaise 15 min to 3 h after infusion. Withdrawal of the offending drug usually results in defervescence within 72–96 h, which helps to confirm the diagnosis, but delays of 5–7 days have been observed.

The most common example of fever as an extension of the pharmacologic effect of the drug is the fever observed following chemotherapy for various solid tumors, lymphomas, and leukemias. Cell necrosis and lysis release various pyrogenic substances from damaged cells. The resulting inflammatory response is also accompanied by cytokine activation of the febrile response. Fever commences 2–3 days after chemotherapy and may last for 1 week or more. This early febrile response usually can be distinguished from febrile neutropenia which rarely develops before the 2nd week after chemotherapy.

Fever can also occur within hours after chemotherapy administration, most likely via other mechanisms. For example, a link between cytosine arabinoside (Ara-C) and fever was described in 1972, but the first systematic description was not until 1981 by Castleberry et al., who coined the term "Ara-C syndrome." Four patients with non-Hodgkin lymphoma and two with acute lymphocytic leukemia (ages 4 and 4 months to 16 years and 6 months) exhibited a unique reaction to intravenously administered Ara-C given alone as a part of the previously reported LSA2-L2 treatment protocol. The syndrome was characterized by fever, myalgia, bone pain, and occasionally by chest pain, maculopapular rash, and conjunctivitis (Castleberry et al. 1981).

More recently, a larger retrospective review was performed of 169 courses of high-dose Ara-C treatment (HDAC) administered to 57 pediatric patients. Fever occurred during 113 of the 169 HDAC courses. The fever began an average of 26 h after the start of the first infusion, with the average peak temperature 39.1 °C. In 12 of the 169 courses, an antibiotic was administered because of suspected sepsis during HDAC. All 12 of these patients had negative blood cultures, and the antibiotics were stopped after 1–3 days without relapse of fever (Ek et al. 2005). Similarly, fever after vincristine administration has also been described (Ishii et al. 1988). Interestingly, all patients were in the maintenance phases of therapy, making apoptotic tumor cells an unlikely source.

The exact mechanism of these fevers is unknown. It was previously demonstrated that pro-inflammatory cytokines such as TNF-α, IL-6, and IFN-γ are released during HDAC and probably mediate the reaction, acting as endogenous pyrogens (Ek et al. 2001). In the case of vincristine-associated fever, Kaufmann and colleagues have speculated that in patients treated with large doses of vincristine, the mechanism of fever may occur due to direct hypothalamic stimulation. However, in both of the above reports, hypersensitivity reactions could not be

ruled out, as symptoms were prevented with corticosteroids.

Hypersensitivity is in fact the most common cause of drug fever (Tabor 1986). Despite a large number of available antineoplastic agents, hypersensitivity reactions are not common except with platinum compounds, epipodophyllotoxins (etoposide), asparaginase, taxanes, and procarbazine (Shepherd 2003). Various mechanisms can cause drug fever, including the formation of circulating antibody-antigen complexes and/or a T cell immune response provoked by a drug or its metabolites. Any one episode may involve multiple antigenic determinants and mechanisms. Fever may be the sole manifestation of a hypersensitivity reaction.

As demonstrated, in most cases of fever associated with antineoplastic agents, the fever is self-limiting and can be prevented or alleviated with premedication. However, in rare cases, hyperpyrexia associated with high mortality can occur. Review of the literature reveals reported cases of fatal hyperpyrexia with bleomycin both in patients receiving the drug for the first time and also in patients who had received previous bleomycin therapy (Carter et al. 1983; Leung et al. 1989; Ma and Isbister 1980). In these cases, patients developed severe rigors and chills, with temperatures rising to as high as 42.5 °C.

Blood Transfusion

Cancer patients may develop a fever as a reaction to receiving a blood transfusion. The most common transfusion reaction is a febrile, nonhemolytic transfusion reaction (FNHTR). The clinical manifestations of this reaction include fever, chills, and sometimes mild dyspnea within 1–6 h after transfusion of red cells or platelets. FNHTRs are benign, causing no lasting sequelae, but are uncomfortable and sometimes frightening to the patient. Furthermore, since fever, with or without a chill, also may be the sign of a severe, acute hemolytic transfusion reaction or infection, FNHTRs cannot be ignored.

The management of FNHTRs should include stopping the transfusion and determining whether or not a hemolytic reaction is taking place as well as administration of antipyretics or meperidine for moderate chills and rigors. Leukoreduction of blood products before transfusion can lessen the reaction (Sirchia et al. 1987). The possibility of fever due to receiving blood products can also be lessened by giving patients acetaminophen or antihistamines before the transfusion.

Paraneoplastic Fever

When an infectious etiology of fever is not detected and noninfectious causes of fever are excluded after careful clinical examination, extensive laboratory, and imaging studies, then paraneoplastic fever should be suspected. It is estimated that paraneoplastic origin is the cause of fever in approximately 10–20 % of both immunocompetent patients and cancer patients.

Fever can be a common presentation with many malignancies. Hodgkin's disease has classically been associated with fever. However, acute leukemia, non-Hodgkin's lymphoma, renal cell carcinoma, bone sarcoma, adrenal carcinoma, neuroblastoma, and pheochromocytoma are also associated with paraneoplastic fever (Pizzo et al. 1982). Solid tumors of the breasts, lungs, and colon do not usually cause paraneoplastic fever, but the presence of liver metastases from these tumors may result in fever (Dalal and Zhukovsky 2006). In addition, any solid tumor causing obstruction can result in fever.

Definition of Paraneoplastic Fever

No clinical features reliably differentiate paraneoplastic fever from fever due to infection, fever associated with collagen-vascular disease, or fever due to other causes. Thus, paraneoplastic fever is often a diagnosis of exclusion, established after a rigorous and thorough work-up of other possible causes of fever in patients with cancer, as discussed above.

Fever due to infection is often characterized by tachycardia, hypotension, and severe chills or rigors. Shock may occur with gram-negative bacteremia. Patients are often in a very toxic state. Proportional tachycardia in response to the degree of fever occurs owing to increased basal metabolic rate and circulatory disturbances.

In contrast, patients with paraneoplastic fever tend to have persistently remittent fevers for long periods of time without much toxic effects though temperatures can be elevated above 40 °C. Chills and tachycardia are infrequent and mild, if present. The usual symptoms are excessive sweating and feelings of warmth. Almost always, paraneoplastic fever is intermittent throughout the day and night. The fever may be short lived or long lasting (Chang 1989). Paraneoplastic fever may persist for more than several months even though complete or partial remission of the cancer is achieved (Chang and Gross 1985).

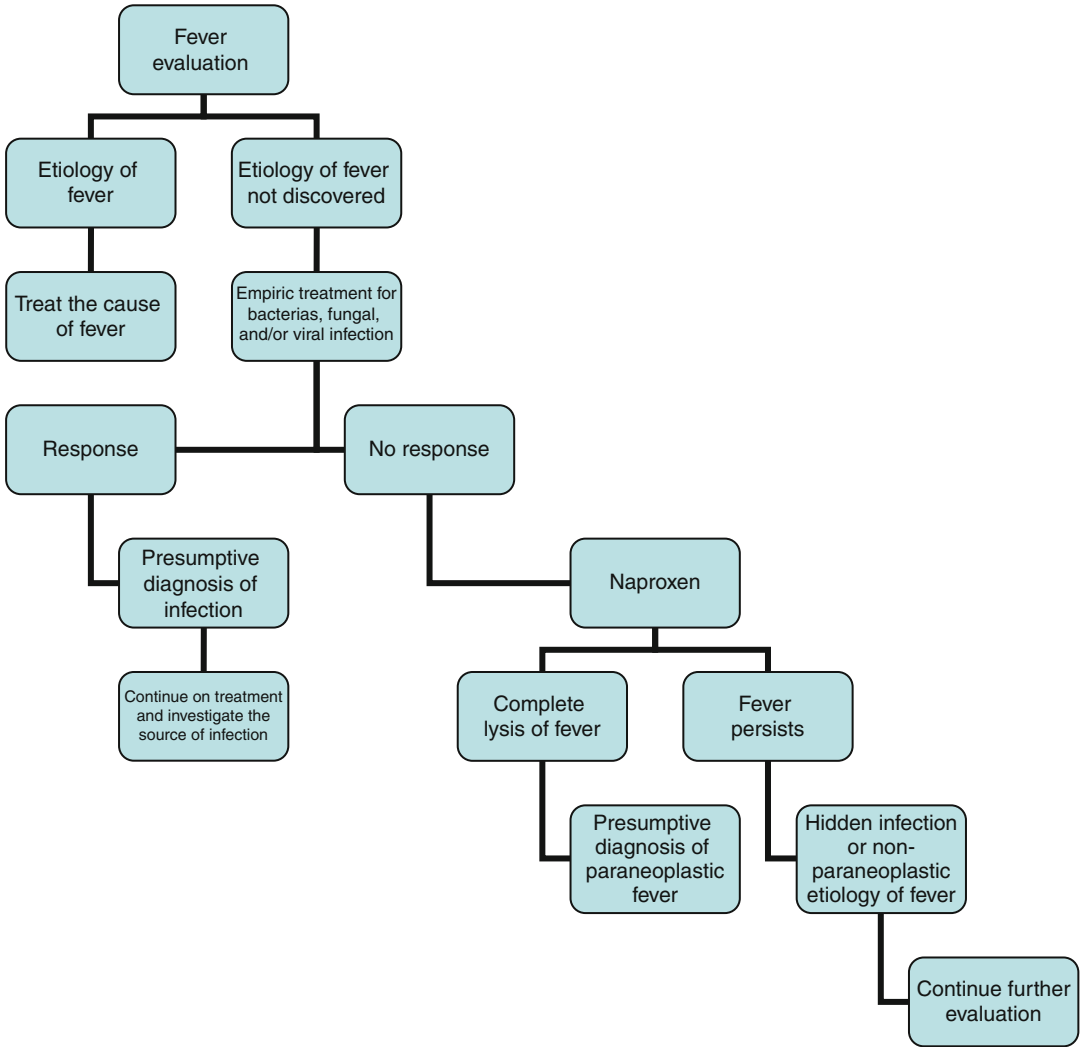
Undoubtedly, establishing the diagnosis of paraneoplastic fever on the basis of clinical findings is difficult. In addition, it should be emphasized that the degree of fever is not a distinguishing feature between infectious and paraneoplastic fevers. Objective methods, other than extensive studies to exclude infections and other causes of fever, have been introduced to help differentiate between fever due to infection and fever due to paraneoplastic fever. The nitroblue tetrazolium test was used to differentiate between fever due to bacterial infection and that due to nonbacterial infection (Feigin et al. 1971; Park et al. 1968). However, this test was later determined to be of uncertain value. In one particular study, the nitroblue tetrazolium test (NBT) showed positive reactions in all of 22 patients with Hodgkin disease and in 9 of 12 patients with malignant lymphoma. No correlation was noted in the degree of NBT reduction, activity of the diseases, presence of fever, leukocytosis, stage of the disease, or treatment modality (Chang et al. 1974).

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly used nonspecific markers of inflammation. These tests have also been investigated as potential markers for differentiating fever due to an infection from paraneoplastic fever. Kallio et al. studied CRP and ESR levels in 66 hospitalized patients (56 with fever due to infection and 10 with paraneoplastic fever) on admission and compared these levels to follow-up CRP levels on hospital day 5. It was determined that CRP and ESR levels at admission were not clinically useful in differentiating paraneoplastic fever from fever due to infection. Interestingly, follow-up CRP levels were significantly lower in patients with fever due to infection when compared with those for paraneoplastic fever (Kallio et al. 2001). More recently, a systematic review of 90 studies summarized the published evidence for an association between circulating concentrations of C-reactive protein (CRP) and cancer. In most studies, CRP concentrations were found to be higher in patients with cancer than in healthy controls or controls with benign conditions. Of the nine large prospective studies identified in this entry, four reported no relationship between circulating CRP levels and breast, prostate, or colorectal cancers, and five studies found that CRP was associated with colorectal or lung cancers. However, the authors of the entry determined that most of the studies evaluating CRP as a diagnostic marker of cancer did not present relevant statistical analyses and provided no strong evidence for a causal role of CRP in cancer (Heikkila et al. 2007).

Establishing the Diagnosis of Paraneoplastic Fever

For the initial diagnosis of a fever secondary to paraneoplastic cause in a patient with fever of unknown origin, important aspects of the workup should include the careful review of clinical histories of malignancies. Attention should be paid to the presence or absence of night sweats, pruritus after a hot bath or shower, and weight loss – particularly when accompanied by a dramatic decrease in appetite. A thorough physical examination should include evaluation for abnormalities of the cranial nerves, the eyes, the throat, heart murmur, adenopathy, hepatosplenomegaly, sternal tenderness, and bone tenderness (Cunha 2007).

Ascertaining the diagnosis of paraneoplastic fever in patients with an established diagnosis of cancer should also include a careful clinical history and physical examination. In addition, the appropriate laboratory studies and imaging studies should be ordered. After these initial diagnostic steps, the following decision tree is recommended (Fig. 1).



Cancer and Fever, Fig. 1 Proposal for the diagnosis of paraneoplastic fever in patients with cancer (Adapted with permission from Chang 1989)

While awaiting laboratory results, empiric treatment with standard broad-spectrum antibacterial agents, combined with or without antifungal agents and vancomycin in certain circumstances, is warranted for at least 7 days. During this time, the clinical response and the febrile response should be followed closely. If the patient has an improved clinical response, the antibiotic therapy should be continued, even if a source of infection has not been identified (Zell and Chang 2005). If no resolution of fever occurs after empiric antibiotics and there are no contraindications (i.e., severe thrombocytopenia or allergy to nonsteroidal anti-inflammatory medications), the naproxen test can be initiated with 375 mg orally every 12 h, for at least a 36-h period (Chang 1989). The complete resolution of fever indicates a positive response to the naproxen test, which would establish a presumptive diagnosis of paraneoplastic fever. A summary of proposed criteria for establishing the diagnosis of paraneoplastic fever is shown in Table 3 (Zell and Chang 2005).

Cancer and Fever, Table 3 Proposed criteria for neoplastic fever (Adapted with permission from Zell and Chang 2005)

I. Temperature >37.8 °C at least once daily
II. Duration of fever over 2 weeks
III. Lack of evidence of infection on the following:
A. Physical examination
B. Laboratory examinations, e.g., cultures from blood, sputum, urine, stool, spinal fluid, pleural fluid, bone marrow, and discharge from local lesions
C. Radiologic examinations, e.g., chest radiographs, computerized tomography of the head, chest, abdomen, and pelvis
IV. Absence of allergic mechanisms such as drug allergy (including chemotherapy), transfusion reaction, and radiation
V. Lack of response of fever to an empiric, adequate trial of antibiotic therapy for at least 7 days
VI. Prompt and complete lysis of fever after the naproxen test, with sustained normal temperature while receiving naproxen

The Naproxen Test

The naproxen test was first described by Chang and Gross in 1984 as a reliable method in assisting in the differential diagnosis of infectious fever and paraneoplastic fever in patients with cancer and fever of undetermined origin. Twenty-two patients with cancer and fever of undetermined origin for more than 7 days were treated with naproxen 250 mg twice daily to control fever when there was no evidence of infection after a careful evaluation. Moreover, in most of these cases, antibiotic therapy had failed to resolve fevers. In this report, 14 of 15 patients with paraneoplastic fever had a complete, sustained lysis of fever while being treated with naproxen. None of five patients with infectious fever had responses to naproxen. In those patients with paraneoplastic fever, lysis was complete within 24 h, and the afebrile state continued as long as the patients were maintained on naproxen (Chang and Gross 1984).

Other nonsteroidal anti-inflammatory drugs such as indomethacin, ibuprofen, and diclofenac have also been shown to be useful in treating paraneoplastic fever. In a randomized trial of naproxen, indomethacin, or diclofenac used to ameliorate cancer-induced fever, all three drugs were equally effective in bringing the temperature down to normal. Naproxen had the most rapid effect (Lusch et al. 1968; Tsavaris et al. 1990).

Corticosteroids have been shown to cause suppression of fever caused by various etiologies, including allergic reactions, collagen-vascular diseases, and malignancy. The antipyretic effect of corticosteroids was compared to naproxen for treating paraneoplastic fever (Chang 1988). In a retrospective study of 39 patients with advanced cancer and established diagnosis of paraneoplastic fever, treatment with naproxen led to defervescence in 36 patients. Twelve of these patients also received corticosteroids at another time; all had previously responded with complete lysis of fever to naproxen. Corticosteroids induced complete lysis in only six of these patients. Though the sample size was small, these observations suggest that naproxen is more effective than corticosteroids as an antipyretic agent in the management of paraneoplastic fever.

Utility of the Naproxen Test

Follow-up data on the efficacy of the naproxen test included a total of 68 cancer patients with FUO. Statistical analysis of these data provides insight into the value of the naproxen test. In the previously mentioned report, the prevalence of paraneoplastic fever was 74 % (50 of 68 patients). The other patients described included those with infectious fever, autoimmune disease-related fever, and radiation-related fever. In the group of patients with paraneoplastic fever, 46 had complete responses, two had partial responses, and two patients had no response to naproxen. Of the 13 patients with infectious fever, all but one had no response to naproxen (Chang 1987).

Based on this data, the sensitivity and specificity of the naproxen test has previously been calculated: sensitivity is 92 % (95 % CI, 80–97 %), specificity is 100 % (95 % CI, 78–100 %), the positive predictive value is 100 % (95 % CI, 90–100 %), and the negative predictive value is 82 % (95 % CI, 59–94 %). Therefore, in a patient with a high clinical suspicion of paraneoplastic fever, the naproxen test

is highly predictive of true paraneoplastic fever (Zell and Chang 2005).

Given the high specificity of the test, if naproxen administration fails to result in complete defervescence of the patient, other etiologies need to be sought. It is still possible that a hidden or masked infection, for example, may be present. A meticulous work-up should be continued.

As an example, a 63-year-old Filipino male was undergoing treatment for acute myeloid leukemia at the local academic institution. Prior to induction with standard idarubicin and cytarabine chemotherapy, he was afebrile. However, on day #16 status-post chemotherapy, when pancytopenia had developed, the patient began to have daily fevers, as high as 39.3 °C. An extensive work-up for an infectious etiology included blood, urine, and sputum cultures, as well as computed tomography (CT) imaging of the chest, abdomen, and pelvis. Broad-spectrum antibiotics were started immediately. And yet, fevers persisted. A bone marrow biopsy performed on day #25 showed no evidence of leukemic cells. At that time, the patient was given naproxen 375 mg q12 h for 3 days. However, fevers continued, which prompted further work-up, including a lumbar puncture and transesophageal echocardiogram – neither of which revealed an infectious source. He felt clinically well, aside from poor appetite.

He did have notable findings of rising liver function enzymes. Finally, approximately 1 month after his daily fevers began, the patient underwent laparoscopic exploratory laparotomy. The surgeons noted white nodules on the gallbladder and spleen and biopsied several sites. One week later, these biopsies grew mycobacterium in culture. He had defervescence soon after treatment was initiated with ritampin, isoniazid, pyrazinamide, ethambutol (RIPE) and clarithromycin (Fig. 2).

In this complicated case, the patient's fevers could easily have been attributed to his leukemia. However, the negative naproxen test prompted the treating physicians to continue a painstaking search for a cause of fevers, ultimately requiring an invasive procedure for diagnosis. Without the naproxen test, the patient might have gone on to receive consolidation chemotherapy, putting him at great risk in the setting of serious occult infection.

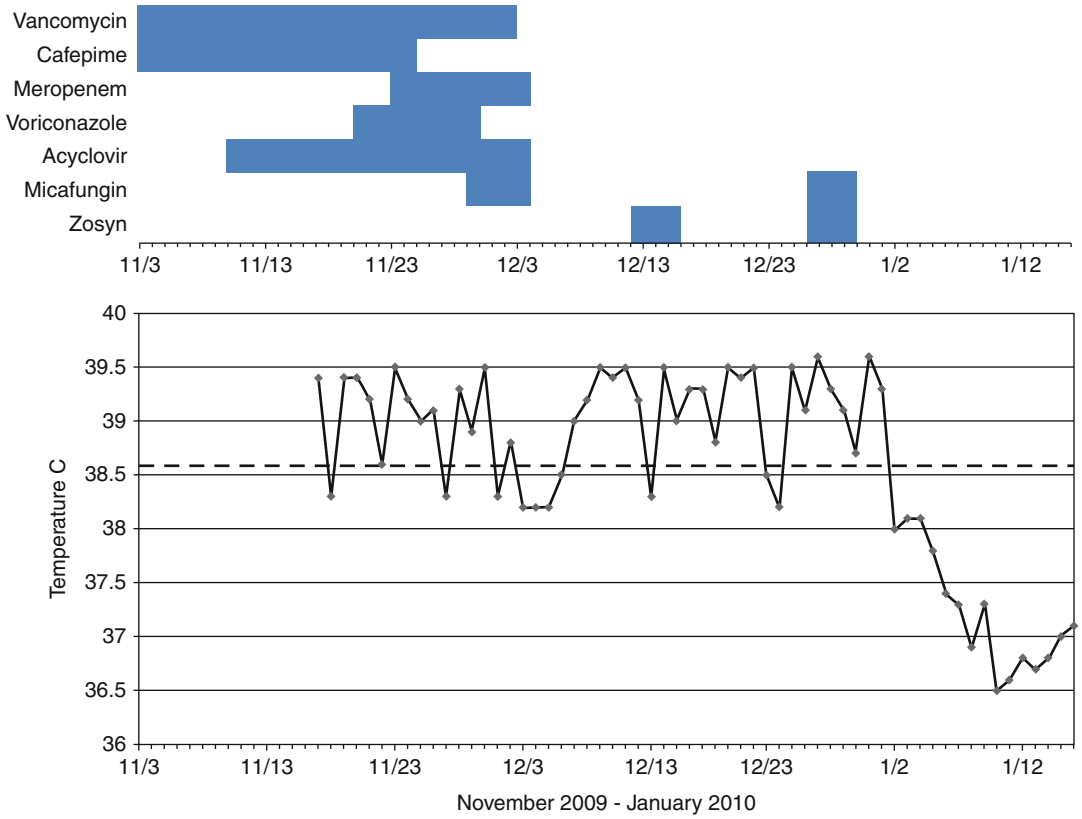
The usefulness of the naproxen test has been confirmed by others in patients with paraneoplastic fever associated with gynecologic malignancies. In one study, naproxen (250 mg orally every 8 h) was given to 12 patients with daily fevers for at least 3 days and negative work-up for infection. Within 24 h of starting naproxen therapy, 10 patients' fever responded, with subjective improvement in patient malaise and fatigue. Two patients did not respond to naproxen therapy in 24 h; thus, it was stopped and the fever work-up was continued. Of these two patients, one was eventually diagnosed with bacteremia after multiple negative blood cultures and initially no response to antibiotics (Economos et al. 1995).

Palliating Paraneoplastic Fever

Fever in patients with cancer can be extremely troubling. It is often associated with fatigue. In addition, as illustrated in the above case, fever with an unknown source demands thorough clinical examinations and a myriad of diagnostic tests which do not always carry a benign risk. Disease-specific chemotherapy may alleviate paraneoplastic fever, if the tumor is responsive to the treatment.

These findings indicate that nonsteroidal anti-inflammatory drugs can provide safe and effective palliation for distressful paraneoplastic fever as well. If naproxen is used, clinicians need to be mindful of weighing the symptomatic benefits against possible side effects such as gastritis and gastrointestinal bleeding. In addition, naproxen is to be used with caution in patients with thrombocytopenia. Other relative contraindications for naproxen use may include cardiac, renal, and hepatic dysfunction.

In some patients, paraneoplastic fever will recur if naproxen is discontinued after a short-term treatment. In a study of recurrent fever in patients with paraneoplastic fever, though naproxen induced sustained fever lysis in some



Cancer and Fever, Fig. 2 Febrile course of a 63-year-old male with acute myelogenous leukemia. Following induction chemotherapy, the patient as expected became pancytopenic but also developed unexplained fever for more than 1 month. The naproxen test on December 1 did not result in resolution of fever, prompting further work-up. After diagnosis of tuberculosis, treatment was initiated on December 29 (Figure courtesy of M. Bryan Shieh)

patients, the fever returned to pretreatment levels in a small subset of patients after naproxen withdrawal. This recurrence typically happened within 24 h after withdrawal. A detailed history taking may reveal the patient has not been compliant with naproxen. Retreatment typically results in complete and sustained fever lysis. However, if the fever is not resolved, reevaluation for infection and other causes is necessary.

Conclusions

Patients with cancer often have complicated medical courses. They can be plagued by symptoms and side effects not only from the primary malignancy but from the cancer treatment itself – whether the modality is antineoplastic, immunologic, targeted, or radiation therapy. If fever occurs, the differential diagnosis will be broad and the treating physician must work carefully through the complexities of the case to come to a solution. Especially in the case of febrile patients with cancer, establishing the correct etiology to fever in a timely manner is paramount to reducing morbidity and mortality.

As the majority of fever in cancer patients is related to infection, thorough clinical evaluations and microbiologic studies should be able to provide the diagnosis; appropriate antibiotics would resolve the fever. However, some patients do not

have responses to antibiotics, and an infectious cause cannot be identified. In these situations, it will be crucial to be able to differentiate infectious fever from paraneoplastic fever.

In difficult circumstances, the naproxen test is an additional useful agent when working through the differential diagnosis of a febrile cancer patient. This inexpensive and relatively safe medication produces complete lysis of paraneoplastic fever. It can be both a valuable diagnostic and therapeutic tool for physicians confronting fever of unknown origin.

Cross-References

- Cancer and the Central Nervous System
- Chemokines
- Interleukin-6
- Paraneoplastic Neurological Syndromes, Overview

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Cancer and Joint Pain

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Definition

Musculoskeletal disorders associated with malignancy may be classified as due to (A) direct tumor involvement of bones, joints, and muscles; (B) paraneoplastic syndromes; (C) altered immune surveillance; and (D) adverse reactions to anticancer therapy. Paraneoplastic rheumatic disorders are those cancer-associated rheumatic syndromes that occur at a distance from the primary tumor or metastases, and induced by the malignancy through hormones, peptides, autocrine and paracrine mediators, antibodies, and cytotoxic lymphocytes. Paraneoplastic rheumatic disorders may precede the diagnosis of the underlying tumor, occur at the same time as the tumor becomes manifest, or arise when metastases develop. In contrast to paraneoplastic syndromes, malignant transformation in the course of certain rheumatic disorders is the result of immune dysregulation; the time interval between the onset of the rheumatic disorder and diagnosis of the secondary malignancy may be as long as 20 years (Naschitz 2001; Andras et al. 2006).

Diversity of Clinical Syndromes

An expanding array of rheumatic disorders is associated with cancer (Naschitz 2001; Andras et al. 2006; Naschitz and Rosner 2008), ranging from the well-established connections with hypertrophic osteoarthropathy, cancer polyarthritis, dermatomyositis, and palmar fasciitis with polyarthritis to various more recently described associations (Table 1). Clinically, it may be difficult to distinguish paraneoplastic rheumatic disorders from direct involvement of the articular and periarticular structures by tumor.

Cancer and Joint Pain, Table 1 The spectrum of paraneoplastic rheumatic disorders[a]

Arthropathies
Local articular involvement by cancer
Rheumatoid arthritis
Cancer polyarthritis
Hypertrophic arthropathy
Polymyalgia rheumatica and atypical polymyalgia rheumatica
Palmar fasciitis and arthritis
Gout
Relapsing polychondritis
Remitting seronegative symmetrical synovitis with pitting edema
Sacroiliitis
Adult-onset Still's disease
Muscular disorders
Dermatomyositis, polymyositis, and dermatomyositis sine myositis
Localized nodular myositis
Necrotizing myopathy
Lambert-Eaton myasthenic syndrome
Scleroderma, panniculitis, and fasciitis
Systemic sclerosis
Eosinophilic fasciitis and fasciitis-panniculitis syndrome
Erythema nodosum
Panniculitis-arthritis
Vasculitides
Miscellaneous rheumatic syndromes
Reflex sympathetic dystrophy
Sjogren's syndrome
Osteomalacia
Skeletal hyperostosis
Antiphospholipid antibody syndrome
Cryoglobulinemia
Erythromelalgia

[a]Adopted from Naschitz (Naschitz 2001)

Evidence of Causality

Interpretation of causal determinism between malignancy and rheumatic disorders is affected by a number of potential sources of error. First, small series of patients are biased toward a positive association. Second, when patients, but not controls, are drawn from a hospital referral population, a "Berkson's bias" may be present, in which the possibility of referral of a patient with both a primary rheumatic disorder and malignancy is much higher than for a patient with a rheumatic disorder alone. Third, ascribing causality based only on the statistical strength of an association between two disorders, as illustrated by standardized incidence ratio (SIR) or odds ratio (OR), may be misleading, because a mere connection between two disorders does not prove causality. An association between two disorders may occur by chance or may reflect a causal relationship other than the one it suggests. For evaluation of a causal relationship between cancer and rheumatic disorders, beyond the strength of the association, additional features of the relationship need to be assessed. Sir Austin Bradford Hill proposed criteria to establish an argument of causation, and these criteria have since been widely applied (Villa et al. 2000; Hill et al. 2001).

Bradford Hill's criteria have been summarized as including (1) the demonstration of a strong association between the causative agent and the outcome; (2) consistency of the findings across research sites and methodologies; (3) the demonstration of specificity of the causative agent in terms of the outcomes it produces; (4) the demonstration of the appropriate temporal sequence, so that the causative agent occurs prior to the outcome; (5) the demonstration of a biological gradient, in which more of the causative agent leads to a poorer outcome; (6) the demonstration of a biologic rationale, such that it makes sense that the causative agent causes the outcome; (7) coherence of the findings, such that the causation argument is in agreement with what we already know; (8) experimental evidence; and (9) evidence from analogous conditions.

These nine Bradford Hill criteria give a measure of the degree in which evidence of causality between a factor and a disease may be established. However, there is no accepted scoring system of the Bradford Hill criteria. Temporal relationship is the only absolutely essential criterion, inasmuch as exposure always precedes the outcome. Clinical judgment is important when considering the guidelines together. In spite of their inherent limitations, the Bradford Hill criteria have been extensively utilized for differentiating causality from association. Two studies

applied the Bradford Hill criteria to cancer-associated musculoskeletal disorders (Naschitz and Rosner 2008; Villa et al. 2000).

Paraneoplastic Rheumatic Syndromes

In applying the Bradford Hill criteria to the association of rheumatic syndromes with cancer, Villa et al. (Villa et al. 2000) found good evidence that solid tumors are determinants of dermatomyositis (based on temporality, strength, consistency, plausibility, coherence, and analogy). The evidence that solid tumors are determinants of polymyositis was not convincing (only temporality, plausibility, coherence, and analogy criteria were satisfied).

The literature abounds in case reports and small case series describing associations between musculoskeletal disorders and cancer. However, the available database is usually insufficient for statistical analysis or judgment of causality based on Bradford Hill criteria. Based on clinical impression, but not yet supported by sufficient evidence, the following rheumatic syndromes may be paraneoplastic in nature: hypertrophic osteoarthropathy, cancer polyarthritis, palmar fasciitis and polyarthritis, and relapsing seronegative symmetric synovitis with pitting edema (Naschitz 2001; Andras et al. 2006; Guegan et al. 2006; Liozon et al. 2006).

Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy is a prototype of rheumatic paraneoplastic syndrome (Naschitz 2001; Andras et al. 2006). The syndrome consists of clubbing of the phalanges; stiffness and swelling of joints, especially the wrists, ankles, and interphalangeal articulations; evidence of periosteal and subperiosteal new bone formation along the shaft of long bones and phalanges on radiographs; and increased vascular endothelial growth factor (VEGF) in the blood. Approximately 90 % of cases are paraneoplastic, with the remaining cases found in association with conditions such as pulmonary fibrosis, endocarditis, Graves' disease, and inflammatory bowel disease. Hypertrophic osteoarthropathy is associated with bronchial carcinoma, lung metastases, and pleural mesothelioma. Resection of the tumor is often followed by remission of the arthropathy and decrease in plasma VEGF. Other treatment options include bisphosphonates, opiate analgesics, nonsteroidal anti-inflammatory drugs, and localized palliative radiation.

Cancer Polyarthritis

Cancer polyarthritis arises predominantly in the elderly and may be oligoarticular or polyarticular, sometimes resembling adult-onset Still's disease or rheumatoid arthritis. Cancer polyarthritis differs from typical rheumatoid arthritis by generally occurring in elderly patients, having an explosive onset, being more often seronegative and asymmetric, and having no family history of rheumatoid arthritis. The lower extremities are usually involved, sometimes with sparing of the small joints of the hands and wrist. The patient does not exhibit rheumatoid nodules. Cancer polyarthritis is often refractory to conventional treatment such as NSAIDs and steroids. Lung cancer is the most common association. The onset of arthritis can precede the diagnosis of cancer by several months. Remission of the arthritis after successful treatment of the neoplasia is the post factum proof of the paraneoplastic nature of the arthritis. Only a few case series of patients with paraneoplastic arthritis have been published. A recent nationwide study from France recruited 26 patients, with a mean age 57.5 years. All had symmetrical polyarthritis involving wrists and hands (85 %). Extra-articular symptoms occurred in 84 %. There was no specific biologic or radiographic feature. The delay between the diagnoses of rheumatism and neoplasia was up to 21.2 months, with a mean of 3.6 months. Tumors were usually diagnosed after articular symptoms occurred (88.5 %). Twenty patients had a solid cancer, usually pulmonary adenocarcinoma, and six had a hematological malignancy. The tumors were diagnosed at an early stage, which may explain the relative long median survival of 1.21 years, with a mean follow-up of 1.9 years. The percentage of resolution of the articular symptoms is higher in patients with solid tumors, as compared to patients with hematological malignancy. In cases of tumor relapse, the rheumatic symptoms did not recur (sic) in 75 % of patients (Morel et al. 2008).

Palmar Fasciitis and Polyarthritis Syndrome

Palmar fasciitis ranges from diffuse globular swelling with warmth and erythema to Dupuytren's contracture. Rheumatoid factor and antinuclear antibodies are negative. This syndrome was described in association with carcinoma of the ovary, endometrium, stomach, breast, prostate, chronic lymphocytic leukemia, and Hodgkin's disease. The shoulders, metacarpophalangeal, and proximal interphalangeal joints are involved. Magnetic resonance imaging and biopsy of palmar nodules reveal inflammation and fibrosis. Anti-inflammatory treatment is usually ineffective. The rheumatic syndromes may precede tumor diagnosis by months. The tumors are often rapidly progressive. Improvement in palmar fasciitis and inflammatory arthritis often occurs following successful treatment of the ovarian carcinoma. Digital contractures, however, may persist. Gynecological examination is warranted in any woman presenting with the sudden onset of unexplained hand pain, palmar inflammatory fasciitis, palmar fibromatosis, and digital contractures (Martorell et al. 2004).

Relapsing Seronegative Symmetric Synovitis with Pitting Edema Syndrome (RS_3PE)

Relapsing seronegative symmetric synovitis with pitting edema syndrome sometimes occurs in association with malignant diseases. The symptoms appear in the form of arthritis and edema surrounding the metacarpophalangeal and interphalangeal joints and wrists. Rheumatoid factor is negative. The patients are generally elderly and male. The associated malignancy may be T cell lymphoma; myelodysplastic syndrome; colon, lung, gastric, prostate, or undifferentiated pelvis cancer; and endometrial carcinoma. In the paraneoplastic forms, symptoms typically are severe and do not respond to the established treatment. Systemic symptoms, such as fever and weight loss, often occur (Naschitz 2001; Guegan et al. 2006).

Relapsing Polychondritis

Relapsing polychondritis is a rare, chronic, inflammatory disease, with episodes of inflammation of the cartilage in the nose, ears, tracheobronchial tree, and joints. It has been reported in association with myelodysplastic syndromes, possibly as an immune response against type II collagen. There have been a few reported cases of relapsing polychondritis associated with malignant lymphoma (Yanagi et al. 2007).

Atypical Polymyalgia Rheumatica

Studies reporting cancer risk after polymyalgia rheumatica and temporal arteritis are few. Between 1965 and 2006, among 35,918 patients hospitalized for polymyalgia rheumatica and temporal arteritis, 3,941 patients developed subsequent cancer, giving an overall SIR of 1.19; for cancer diagnosed later than 1 year of follow-up, the SIR was 1.06. Hence, a marginally increased risk of cancer was noted in the first year after hospitalization (Ji et al. 2010). Clinicians should consider the possibility of underlying cancer in certain instances of polymyalgia rheumatica, although prospective studies do not suggest a general excess incidence of malignancy (Naschitz 2001; Andras et al. 2006). Atypical features such as young age, asymmetrical symptoms, relatively low erythrocyte sedimentation rate, and poor response to corticosteroid treatment should raise the suspicion of bone metastases as the cause of the patients' symptoms that resemble polymyalgia rheumatica.

Malignant Transformation During of Rheumatic Disorders

In contrast to the limited evidence of the occasional paraneoplastic nature of rheumatic syndromes, there is adequate support for the causal determinism between chronic inflammatory disorders and subsequently occurring malignancies.

The Risk of Neoplasia in the Course of Rheumatoid Arthritis

Large population-based studies have found little evidence of an increased risk of carcinoma in rheumatoid arthritis (Ekstrom et al. 2003; Bernatsky et al. 2006). The risk of cancer of the lower gastrointestinal tract may be decreased, possibly attributable to nonsteroidal anti-inflammatory drugs. On the other hand, there is an increased risk for lymphoma occurring late in

the course of rheumatoid arthritis. The largest study supporting this association involved 76,527 patients identified through the Swedish hospitalization database between 1964 and 1999 (Ekstrom et al. 2003). Five hundred and thirty five cases of lymphoma were identified, yielding SIR 2.00. Wolfe found SIR 1.9 for lymphoma among patients with rheumatoid arthritis recruited from rheumatology practices. Using population-based linked registry data from Sweden and Denmark, Landgren found an increased risk of non-Hodgkin lymphoma in patients with rheumatoid arthritis (OR 2.7). In the analysis by Villa et al. (Villa et al. 2000), six Bradford Hill criteria supported determinism of lymphoma by rheumatoid arthritis, including strength, consistency, temporality, plausibility, coherence, and analogy.

Recent studies addressed the pathogenesis of lymphoma during the course of chronic inflammation in general and rheumatoid arthritis in particular (Bernatsky et al. 2006). Nearly all B cell non-Hodgkin lymphomas express the B cell receptor, suggesting that chronic antigen stimulation plays a central role in their emergence. Failure of the antigenic stimulus to subside, as occurs with endogenous autoantigens or with persistent infections, can increase the chance of B cell transformation. Other examples of chronic stimulation by antigens leading to lymphoma include hepatitis C, Helicobacter pylori, and Epstein-Barr virus.

Methotrexate treatment has been linked to lymphomas, often Epstein-Barr virus positive, characterized by spontaneous regression once methotrexate is withdrawn. In patients who were treated by methotrexate for rheumatoid arthritis and developed non-Hodgkin's lymphoma, remission can be observed following methotrexate withdrawal, especially in non-Hodgkin's lymphoma with latency type III Epstein-Barr virus infection. The analysis of Epstein-Barr virus infection, including the latency types, might be useful to decide the optimum therapeutic strategy (Miyazaki et al. 2007). There is also data suggesting an increased risk of malignancies in rheumatoid arthritis patients who were treated with anti-TNF antibody (Breedveld et al. 2006).

Ankylosing Spondylitis

The association between ankylosing spondylitis and malignant lymphomas was assessed in a nationwide, population-based, case–control study of 50,615 cases of lymphoma, and 92,928 matched controls, by using prospectively recorded data on lymphomas from the Swedish Cancer Register (1964–2000) and data on pre-lymphoma hospitalizations for ankylosing spondylitis from the Swedish Inpatient Register (1964–2000). There was no increased risk of lymphoma among patients with ankylosing spondylitis (Askling et al. 2006).

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is associated with a long-term risk of developing malignant lymphoma. The association between SLE and malignancy fulfilled five Bradford Hill criteria demonstrating causality (strength, temporality, plausibility, coherence, and analogy) (Villa et al. 2000).

Systemic Sclerosis

The association between systemic sclerosis and malignancy fulfilled six Bradford Hill criteria in Villa's study (strength, consistency, temporality, plausibility, coherence, and analogy); the authors concluded that there is evidence of causality between systemic sclerosis and lung cancer (Villa et al. 2000).

Sjogren's Syndrome

An increased risk of developing lymphoma has been identified in Sjogren's syndrome (Soderberg et al. 2006). The association between Sjogren's syndrome and lymphoma fulfilled six Bradford Hill criteria (strength, consistency, temporality, plausibility, coherence, and analogy); the authors concluded that there is evidence of causality between Sjogren's syndrome and lymphoma (Villa et al. 2000).

Which Work-Up for Which Patients?

Paraneoplastic musculoskeletal disorders may precede the diagnosis of cancer by months or years, thus representing a potential marker for occult malignancy (Naschitz 2001; Andras et al. 2006). Diagnosing some of those syndromes may

be challenging because certain paraneoplastic musculoskeletal disorders are rare and the clinician's opportunity to gain experience with such syndromes is limited. The prevalence of paraneoplastic rheumatic syndromes in a cohort of 3,770 patients with newly diagnosed solid tumors was 2.65 %, with arthritis and Raynaud's prevailing: both paraneoplastic syndromes were linked to malignancies of the urogenital system. The patients' immunologic status did not help differentiate between paraneoplastic and other arthritides (Rugienė et al. 2011). Further difficulty stems from the fact that paraneoplastic rheumatic syndromes may be clinically indistinguishable from disorders caused by infiltration of musculoskeletal organs by cancer cells, whether primary or metastatic. It is generally accepted that an extensive search for malignancy in most patients with recent-onset musculoskeletal disorders of unknown etiology is not cost-effective and thus not to be recommended, unless a patient presents additional findings suggestive of malignancy. Rheumatic syndromes that may be clues of occult neoplasia have been reviewed elsewhere (Naschitz 2001; Andras et al. 2006).

The question of whether "tumor markers" and markers of altered immunity may be useful in the work-up of patients with recent-onset musculoskeletal disorders has not been settled (Rugienė et al. 2011). Recent studies revealed a layer of genetic programmatic coordination by which cells determine their fate; this layer involves posttranscriptional regulation of gene expression by microRNAs. Defining the molecular taxonomy of tumors by microRNAs patterns and applying molecular taxonomy patterns to the diagnosis of neoplasia are tasks for future studies.

An increased incidence of antinuclear antibodies (ANA) has been detected in malignant conditions, but no ANA specificities (anti-ENA, anti-DNA) have been recognized in patients with malignancies. Hypocomplementemia was present in a quarter of patients with Sjogren's syndrome and correlated with lymphoproliferative disorders and mortality (Ramos-Casals 2004). Circulating monoclonal immunoglobulins were detected in one-fifth of patients with Sjogren's syndrome, most commonly monoclonal IgG (Brito-Zeron et al. 2005). Relevance of the latter immunologic finding for diagnostic purposes has not been established (Naschitz 2001; Andras et al. 2006).

Conclusions

There is firm epidemiologic evidence that cancer may present with paraneoplastic dermatomyositis, less so for polymyositis. Additionally, there is a prevailing clinical impression, but scarce epidemiological evidence, that certain musculoskeletal disorders may be paraneoplastic in nature. The role of specific clinical findings and biological markers, as hints of a possible neoplastic etiology of musculoskeletal syndromes, has not been solved. Strong evidence has accumulated on the role of longstanding rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, and systemic sclerosis as premalignant conditions.

Cross-References

- ▶ Cancer and Dermatomyositis
- ▶ Cancer and Joint Pain
- ▶ Cutaneous Vasculitis
- ▶ Giant Cell Arteritis
- ▶ Raynaud's Phenomenon
- ▶ Scleroderma-Like Conditions of the Skin

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Cancer and Nephrotic Syndrome

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Synonyms

Focal segmental glomerulonephritis; IgA nephropathy; Light chain nephropathy; Membranoproliferative glomerulonephritis; Membranous glomerulonephritis; Minimal change disease; Paraneoplastic glomerulonephritis; Rapidly progressive glomerulonephritis; Renal amyloidosis

Definition and Background

Nephrotic syndrome describes the onset of heavy proteinuria (>3.0 g/24 h), hypertension, hypercholesterolemia, edema, and microscopic hematuria. The term *nephrotic range proteinuria* is used when patients demonstrate heavy proteinuria without the aforementioned clinical manifestations. Nephrotic syndrome has been described in a number of renal syndromes including but not limited to minimal change disease (MCD), focal segmental glomerulonephritis (FSGS), membranous glomerulonephritis, and renal amyloidosis (Lewis and Neilson 2012).

Nephrotic syndrome is a rare complication of both solid and hematologic malignancies that is often described as a paraneoplastic syndrome. Paraneoplastic nephropathies are not directly related to tumor burden, invasion, or metastasis, but are caused by the secretion of hormones, growth factors, cytokines, and tumor antigens by the tumor itself (Ronco 1999). The first series of paraneoplastic glomerulonephritis was published by Lee et al. in 1966 (Lee et al. 1966).

While membranous nephropathy in patients with solid tumors and minimal change disease in patients with Hodgkin's lymphoma are considered the classic glomerulonephropathies associated with malignancy, cancer-associated nephrotic syndrome encompasses a plethora of glomerulonephropathies including FSGS, membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, and rapidly progressive glomerulonephritis (RPGN). Paraneoplastic glomerulonephritis improves with the remission of the underlying malignancy. Therefore, early recognition of these disorders is important as treatment differs from idiopathic glomerulonephropathies. While paraneoplastic glomerulonephritis must be considered if nephrotic range proteinuria occurs in the setting of malignancy, diagnosis is established when proteinuria remits with treatment of the malignancy and/or recurs with recurrence of the underlying malignancy (Lefaucheur et al. 2006; Bacchetta et al. 2009).

Solid Tumors

Membranous Nephropathy

Membranous nephropathy has been most consistently linked to malignancy. The largest series of patients with membranous nephropathy demonstrated a 10 % prevalence of cancer (Lefaucheur et al. 2006). Paraneoplastic membranous nephropathy is more comment in older individuals (age >50), current or former tobacco users (>20 pack-year history), and male gender (Lefaucheur et al. 2006; Ronco 1999). Membranous nephropathy has been seen most commonly in prostate adenocarcinoma and lung carcinoma; however, it has also been reported in breast carcinoma, renal cell carcinoma, gastric adenocarcinoma, colon adenocarcinoma, neuroblastoma, neuroendocrine tumors, GIST, hepatocellular carcinoma, choriocarcinoma, carcinoid tumor, and nasopharyngeal carcinoma (Becker et al. 1996; Lefaucheur et al. 2006; Wagrowska-Danilewicz and Danilewicz 2011).

On pathology, membranous nephropathy is characterized by subendothelial immune complex deposition. An autopsy series of patients with malignancy demonstrated that 17 % of kidneys contained glomerular deposits on immunofluorescence (Beaufils et al. 1985). Another series suggests that by electron microscopy, 55 % of patients with cancer have immune complex deposition consistent with membranous nephropathy (Pascal et al. 1976). While carcinoembryonic antigen, prostate-specific antigen, and melanoma antigens have been associated with membranous nephropathy, it is not clear that they are the causative agents. Ohanti et al. demonstrated that patients with paraneoplastic membranous nephropathy have significantly more IgG1 and IgG2 deposition compared to those with idiopathic membranous nephropathy. However, IgG4 was equally expressed in both paraneoplastic and idiopathic membranous nephropathy (Ohtani et al. 2004). As IgG1 and IgG2 formation is regulated by the type 1 T-helper (Th1) cell release of cytokines (i.e., IL-12 and interferon), some hypothesize that Th1-mediated responses in malignancy may drive membranous nephropathy (Ohtani et al. 2004; Lien and Lai 2011).

Minimal Change Disease (MCD)

MCD has been observed in lung, colorectal, and renal cancers. Some theorize that MCD in malignancy may be related to increased expression of vascular endothelial growth factor (VEGF). This is supported by pediatric studies that show increased VEGF expression in the podocytes of patients who have nephrotic syndromes (Ostalska-Nowicka et al. 2005). VEGF has been associated with increased membrane permeability (Taniguchi et al. 2004). Taniguchi et al. reported a case in which a patient with rectal adenocarcinoma had elevated VEGF and nephrotic syndrome at diagnosis; however, after resection of the tumor, proteinuria resolved and VEGF normalized.

Membranoproliferative Glomerulonephritis (MPGN)

MPGN has been rarely reported in lung, renal, and gastric cancers. While some cases have demonstrated improvement in nephrotic syndrome with resection of the malignancy, others have

improved with prednisone (Ahmed et al. 2008). Therefore, some hypothesize that MPGN may be associated with immune complex deposition induced by tumor antigens.

Rapidly Progressive Glomerulonephritis (RPGN)

RPGN has been reported in renal call, lung, and gastric cancers. However, many of the cases reported were prior to elucidation of anti-neutrophil cytoplasmic antibodies (ANCA). It is known that ANCA-associated vasculitides carry a higher risk for development of malignancy. Additionally, cases in which RPGN resolved with treatment of the underlying malignancy inevitably required immunosuppressive therapy, which would concomitantly treat an underlying vasculitis (Lien and Lai 2011). The correlation between RPGN and malignancy is less clear.

IgA Nephropathy

IgA nephropathy has been identified in patients with carcinomas of the respiratory tract, nasopharynx, and renal cell. There have been cases of Henoch-Schonlein purpura in lung cancers and other malignancies (Pertuiset et al. 2000; Flynn et al. 2011). Anticancer therapy has been used to treat this disorder but the pathophysiology of paraneoplastic IgA nephropathy is not well understood (Mustonen et al. 1984).

Thrombotic Microangiopathy

Thrombotic microangiopathy is characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic alteration, and acute kidney injury. It is believed to be caused by microvascular tumor emboli. Therefore, thrombotic microangiopathy is not classified as a paraneoplastic syndrome, but often presents with nephrotic range proteinuria as well. It has been described in gastric, lung, and breast cancers and carries a poor prognosis. In the Oklahoma thrombocytopenic thrombotic microangiopathy (TTP)/hemolytic uremic syndrome (HUS) registry, 10 patients with cancer-associated thrombotic angiopathy were identified; none of these patients improved with plasma exchange, and all died after diagnosis. This demonstrates that thrombotic microangiopathy causing nephrotic syndrome carries a different pathophysiology compared to TTP.

Hematologic Malignancies

Minimal Change Disease (MCD)

MCD occurs in approximately 1 % of patients with Hodgkin's lymphoma. It has also been reported in chronic lymphocytic lymphoma (CLL), even in early stage disease (Alzamora et al. 2006), myelodysplastic disorders, and in thymomas as well, particularly lymphocyte-predominant thymomas. In the post-allogeneic transplant setting, appearance of MCD is considered to be a presentation of graft-versus-host disease (GVHD), as donor T cells have been observed to infiltrate the renal parenchyma (Romagnani et al. 2005). Immunosuppressive treatment for GVHD has also improved proteinuria in these cases (Silva et al. 2007).

In Hodgkin's lymphoma, MCD has been associated with increased inflammatory markers, particularly type 2 T-helper cell (Th2) cytokines. In a rat model, it has been shown that overexpression of IL-13 (a Th2 cytokine) results in a MCD-like nephropathy (Lai et al. 2007). It is known that IL-13 is also overexpressed in Hodgkin's disease (Ohshima et al. 2001). While there appears to be an association between IL-13 and MCD, it is not clear whether IL-13 itself directly causes increased membrane permeability that results in MCD. The relationship between Th2 response and MCD has been further demonstrated in thymomas. In lymphocyte-predominant thymomas, MCD persists even after tumor excision and improves with steroid treatment (Karras et al. 2005). Rat models of thymoma show a similar phenomenon in which MCD persists despite thymectomy. In these rats, there is increased Th2-mediated cytokines, and suppression of the Th2 axis improves the degree of proteinuria (Le Berre et al. 2005). Models in thymoma and Hodgkin's disease suggest that regulation of the Th2 axis may be helpful in the treatment of MCD.

Focal Segmental Glomerulonephritis (FSGS)

FSGS occurs in 0.1 % of patients with Hodgkin's lymphoma and in approximately 3 % of patients with myeloproliferative disorders (e.g., polycythemia vera, essential thrombocythemia). It has also been seen in myelodysplastic disorders. Patients with high platelet counts in particular have elevated platelet-derived growth factor (PDGF), which has been found to enhance mesangial proliferation and fibrosis in vitro (Gersuk et al. 1989). Supporting this hypothesis, PDGF is not elevated in chronic myelogenous leukemia that is not associated with FSGS (Floege et al. 2008).

Membranoproliferative Glomerulonephritis (MPGN)

MPGN has been seen in CLL, non-Hodgkin's lymphomas, and hairy cell leukemia. Some cases have been associated with a mixed cryoglobulinemia (types I and II) involving a monoclonal immunoglobulin. Additionally, patients with hepatitis C-associated mixed cryoglobulinemia whose proteinuria does not respond to traditional hepatitis C therapy have been found to respond to rituximab, an anti-B-cell antibody (anti-CD-20). These findings may imply that B cell proliferation has a role in the development of MPGN (Cacoub et al. 2008).

Membranous Nephropathy

Membranous nephropathy has been rarely seen in CLL, chronic myelomonocytic leukemia, and non-Hodgkin's lymphomas. When it occurs, it presents with subepithelial deposits and monoclonal IgG kappa light chain deposits, suggesting that antibodies produced by monoclonal B cells may play a role in the development of membranous nephropathy (Evans et al. 2003).

IgA Nephropathy

IgA nephropathy has been associated with cutaneous T cell lymphomas. As the Th2 cytokine profile is dominant in cutaneous T cell lymphomas, skewed immunoregulation has been implied in the development of IgA nephropathy in this disorder (Bajel et al. 2009).

Light Chain Related Nephropathy

Both multiple myeloma and amyloidosis cause nephrotic range proteinuria through a number of mechanisms. Kappa and lambda free light chains produced in both disorders are freely filtered across the glomerulus. They overwhelm the ability of the proximal tubule cells to endocytose them. Therefore, they form tubular casts with Tamm-Horsfall protein (uromodulin) that can cause tubular obstruction, which decreases the glomerular filtration rate. It is believed that the Tamm-Horsfall proteins interact with the variable regions of the light chains, which may explain why light chain burden does not correlate directly with the degree of nephropathy (Comenzo et al. 2001). Additionally, the endocytosed light chains in the renal tubule cells induce a proinflammatory response (activation of nuclear factor kappa B and release of IL-6, IL-8, and tumor necrosis factor-a), which subsequently causes deposition of matrix protein that further disrupts glomerular integrity (Sengul et al. 2002). Lastly, the deposition of immunoglobulins themselves, in the form of amyloid and non-amyloid, through every portion of the kidney independently cause nonselective proteinuria (Dimopoulos et al. 2008).

Summary

Both solid and hematologic malignancies are associated with nephrotic range proteinuria through various mechanisms. Specific glomerulonephropathies have been associated with different types of malignancies. It appears that monoclonal formation of antibodies, as well as polarized Th1 versus Th2 responses, are mediators of the development of paraneoplastic glomerulonephropathies. However, the exact pathophysiology underlying these disorders has yet to be better elucidated.

Cross-References

- ▶ IgA Nephropathy
- ▶ Paraneoplastic Neurological Syndromes, Overview

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Cancer and Neuropathies

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Synonyms

Immune-mediated neuropathy in cancer; Inflammatory neuropathy associated with malignancy; Paraneoplastic neuropathy; Peripheral neuropathy in cancer; Polyneuropathy in cancer

Definition

Neuropathy refers to the injury or dysfunction of the peripheral nerves. The peripheral nerves are those that are located outside of the brain and spinal cord, providing sensory, motor, and autonomic innervation to all organs and structures of the body. Depending on the cause of the neuropathy, sensory nerves, motor nerves, and/or autonomic nerve fibers may be affected to varying degrees. As a result, interruption of normal peripheral nerve function can result in pain, tingling, numbness, weakness, clumsiness, gait imbalance, and/or autonomic dysfunction, such as blood pressure fluctuations, temperature dysregulation, and gastrointestinal dysfunction.

Patients with cancer are subject to the development of peripheral neuropathy on a number of bases. Neuropathic dysfunction of the peripheral nerves in patients with cancer occurs most frequently as a side effect of chemotherapeutic agents used for treatment. Additional etiologies include direct tumor invasion of the peripheral nerves or nerve plexi, involvement of spinal nerves in leptomeningeal carcinomatosis, and collateral damage to nerve structures from radiation treatment.

In addition, several *paraneoplastic* syndromes have been identified in which peripheral neuropathy is either the presenting or the predominant characteristic. Paraneoplastic syndromes are broadly defined as a symptom constellation that occurs as a remote effect of cancer on the nervous system, mediated by an immunological process. In some cases, a specific type of neuropathy with characteristic features is associated with an identifiable antibody (*onconeural* antibody) and specific types of tumor. In the malignant plasma cell proliferative disorders, direct activity of monoclonal immunoglobulins is implicated in the pathogenesis of various neuropathies (Antoine and Camdessanche 2007; DeAngelis and Posner 2009).

Basic Characteristics

Paraneoplastic Neuropathy Associated with Onconeural Antibodies

The most widely recognized antibody associated with neuropathy occurring on a paraneoplastic basis is the *anti-Hu antibody*, also referred to as the *antineuronal nuclear antibody-1 (ANNA-1)*. First described by Denny-Brown in 1948, the anti-Hu paraneoplastic syndrome is characterized by sensory neuronopathy and/or encephalomyelitis associated with serum autoantibodies directed against antigens expressed by certain tumors, most commonly small cell lung cancer (Dalmau et al. 1992).

The classical presentation of this disorder is development of an acute-subacute pure sensory neuropathy without motor involvement. It affects women more than men, with an age of onset typically between 50 and 80 years old. Concomitant encephalomyelitis is present in about 25–50 % of cases. Neuropathic symptoms include pain and numbness, often asymmetric at onset, evolving over weeks to months to involve all extremities and occasionally the face and trunk. Sensory ataxia may be severe, affecting the ability to walk or even sit unsupported. Deep tendon reflexes are typically absent. Less commonly, anti-Hu antibodies are implicated in other neuropathy phenotypes, including mixed sensorimotor and predominantly motor neuropathies. Motor weakness of the limbs and rarely face may therefore be present, in rare cases manifesting as the prominent symptom. Dysautonomia and cranial neuropathies, though even more rare, may also occur.

The diagnosis is made by a combination of clinical signs and symptoms as well as detection of anti-Hu antibodies in either the serum or CSF. The majority of patients diagnosed with the syndrome do not have a known cancer diagnosis at the time of onset of the neurological symptoms. The time to definitive diagnosis of identifiable cancer can range from several months to several years. Small cell lung carcinoma accounts for 70–90 % of these cases, though many other cancer types have been implicated, including prostate, breast, ovarian, pancreatic, neuroendocrine, thymic, and bladder.

In addition to anti-Hu, other onconeural antibodies have been associated with specific neuropathy syndromes in patients with cancer.

Anti-CV2 onconeural antibodies have been associated with sensory and sensorimotor neuropathy in the setting of small cell lung cancer and less frequently thymoma and non-Hodgkin's lymphoma. CV2 antibodies are also associated with cerebellar ataxia and uveitis.

Ganglionic nicotinic acetylcholine receptor binding antibodies are associated with a syndrome of acute autonomic neuropathy, presenting with severe orthostatic hypotension, nausea and vomiting after meals, reduced sweating, dry eyes and mouth, sexual dysfunction, and/or bladder dysfunction. In about 20 % of cases, sensory neuropathy is also present, usually prominently affecting the small fiber nerves and manifesting as pain. As with anti-Hu and anti-CV2 neuropathies, this paraneoplastic neuropathy syndrome is also most frequently observed in patients with small cell carcinoma of the lung, although it has also been reported in patients with other malignancies, particularly thymoma (Rudnicki and Dalmau 2005).

The pathophysiology of these syndromes is believed to occur via an immune response triggered by the neoplasm in which an antibody generated against the tumor becomes misdirected toward a tissue that expresses the same (or sufficiently similar) antigen. In the case of the paraneoplastic neuropathies, the antibodies target various sites along the peripheral neurons and/or nerves, resulting in the injury and dysfunction of these structures. This theory is supported by studies showing that in patients with anti-Hu antibodies, tumors tend to be smaller and may even spontaneously regress (Dalmau et al. 1999).

Neuropathies and Plasma Cell Proliferative Disorders

Multiple myeloma, osteosclerotic myeloma, Waldenstrom's macroglobulinemia, as well as other plasma cell dyscrasias are often associated with peripheral neuropathy (as is monoclonal gammopathy of uncertain significance or MGUS). Multiple neuropathy variants occur in disorders associated with monoclonal paraproteins, including inflammatory demyelinating neuropathies, as well as those with features of predominantly axonal injury. Usually, specific autoantibodies known to target peripheral nerve antigens are not identified.

Clinical studies have demonstrated evidence of preexisting peripheral neuropathy in up to 25 % of patients with multiple myeloma prior to their treatment with potentially neurotoxic chemotherapy agents. Osteosclerotic myeloma is a rare variant of myeloma with a very high prevalence of peripheral neuropathy. Many patients with this disorder will present with symptoms of neuropathy, either

as part of the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) associated with this type of cancer or as an isolated feature. The incidence of peripheral neuropathy in Waldenstrom's macroglobulinemia is possibly as high as 47 %.

In the plasma cell dyscrasias resulting in monoclonal gammopathies, it is believed that in some cases the paraproteins react immunologically with specific peripheral nerve or neuron structures, in some cases acting as antibody. In patients with IgM monoclonal gammopathy and neuropathy, antibodies with reactivity directed against the myelin-associated glycoprotein (anti-MAG) may be present. *Anti-MAG* neuropathy predominantly involves sensory nerves, and prominent tremor and sensory ataxia are commonly seen features. Anti-MAG antibodies have been identified in 5–45 % of patients with Waldenstrom's macroglobulinemia. In other cases, IgM or IgG reactivity toward specific ganglioside subtypes is associated with specific phenotypes of neuropathy (Latov 1995; Ropper and Gorson 1998).

Treatment

There are two main modes of treatment for immune-mediated neuropathies associated with cancer: suppressing the immune response and treating the underlying malignancy. Immune suppression typically consists of using corticosteroids, cyclophosphamide, azathioprine, plasma exchange, and/or intravenous immunoglobulin to curb the autoantibody activity directed against the peripheral nerves. Unfortunately, immunomodulatory treatment is often unsatisfactory, leading to stability of symptoms in some patients but only very rarely improvement. Treatment of the underlying malignancy generally yields the greatest improvement. Studies have demonstrated that antitumor therapy is the most significant factor in creating stabilization and improvement in patients with anti-Hu syndrome, and in approximately two-thirds of multiple myeloma patients, the neuropathy responds to successful treatment of the cancer.

Cross-References

- ▶ Cancer and Dermatomyositis
- ▶ Cancer and the Central Nervous System
- ▶ Paraneoplastic Neurological Syndromes, Overview

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Cancer and the Central Nervous System

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Synonyms

Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-prionic acid; AMPA; ANNA; Antineuronal nuclear antibody; Collapsin response mediator protein; CRMP; GABA; GAD; Glutamic acid decarboxylase; Metabotropic glutamate receptor type 1; mGLuR1; NMDA; *N*-methyl-D-aspartate; PCA; Polypyrimidine-tract binding;

PTB; Purkinje cell autoantibody; Tubby-like protein 1; TULP1; VGCC; VGKC; Voltage-gated calcium channel; Voltage-gated potassium channel; γ-Aminobutyric acid-B

Definition

The central nervous system (CNS) may be effected by cancer both directly, through metastatic disease and direct tumor extension, or indirectly. Damage to the nervous system, remote from the site of tumor and not associated with toxicity or metabolic abnormalities associated with cancer or its treatment, is termed paraneoplastic neurological syndromes (PNS). PNS, which are believed to exert their effect through an immune-mediated mechanism (Darnell 1996), may affect any neuronal cell type in the peripheral or central nervous system. While PNS may present as a generalized or diffuse disorder, such as a paraneoplastic encephalomyeloneuritis, there are several recognized or classical clinical syndromes which may affect certain anatomic locations of the central nervous system. The clinical characteristics and pathophysiology of the recognized paraneoplastic syndromes of the CNS, including limbic encephalitis, paraneoplastic cerebellar degeneration, opsoclonus-myoclonus, retinopathies, and stiff person syndrome will be the focus of this entry.

Clinical Presentation and Diagnosis

PNS usually present in an acute to subacute manner, over days to weeks, producing severe disability followed by stabilization. Laboratory evaluation usually demonstrates evidence of inflammation in the cerebral spinal fluid (CSF) such as lymphocytic pleocytosis, elevated protein, and oligoclonal banding, as well as brain magnetic resonance imaging (MRI) abnormalities on fluid attenuation inversion recovery (FLAIR)/T2 sequences. In the majority of cases, the PNS will likely be the initial presentation, the underlying cancer only discovered after a recognized syndrome spurs a search for malignancy.

Key to the diagnosis of PNS is the discovery of antineuronal antibodies in the serum and CSF leading to the postulate of autoimmunity as the pathophysiological basis of PNS. When these antibodies are markers of an underlying cancer, they are termed onconeural antibodies (Musunmuru et al. 2001). Over the years, certain well-characterized onconeural antibodies have been associated with certain clinical presentations representing classic PNS as well as certain underlying malignancies (Table 1). These include anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma2, and anti-amphiphysin. When found, these may help focus the search for cancer to a few organs.

Recently, these onconeural antibodies have been classified as belonging to one of two groups. Antibodies from group 1 are found to target intracellular neuronal antigens; those from group 2 target neuronal surface antigens (Graus et al. 2010). It has proven difficult to produce animal models of disease based on passive transfer of group 1 antibodies, which include the well-characterized onconeural antibodies, suggesting these antibodies are likely not directly pathogenic but may represent the humoral component of a more complex cellular response (Tanaka et al. 2004). Antibodies from group 2, which usually target synaptic cell surface membrane proteins, appear to have a more direct pathogenic role given their good response to immunotherapy, sometimes regardless of disease duration, and correlation of disease response to antibody titer (Dalmau 2011). While there is a strong association in this second group with certain characteristic CNS syndromes, a paraneoplastic syndrome is less certain as there may or may not be an associated malignancy.

Classic PNS of the CNS

While PNS may present with diffuse or multifocal encephalomyeloneuritis, there are certain distinct classical clinical presentations

Cancer and the Central Nervous System, Table 1 Paraneoplastic syndromes of the CNS and associated tumors and antibodies

Clinical syndrome	Associated tumors	Associated antibodies	References
Limbic encephalitis	SCLC, testicular cancer, thymoma, teratoma, Hodgkin's disease, non-SCLC	**Anti-Hu** (ANNA-1), **anti-Yo** (PCA-1), **anti-Ri** (ANNA-2), ANNA-3, anti-Ma1, **anti-Ma2** (Ta), **anti-amphiphysin**, **anti-CRMP5** (CV2), PCA-2, anti-CRMP3, 4, anti-VGKC, anti-NMDAR, anti-$GABA_B$, anti-AMPA	Luque (1991), Knudsen (2007), Dalmau (2007), Gultekin (2000), Lawn (2003), Tuzun (2007), Dalmau (2008), Irani (2011), Boronat (2011), Rosenfeld (2010)
Cerebellar degeneration	Breast cancer, ovarian cancer, SCLC, Hodgkin's disease	**Anti-Yo** (PCA-1), **anti-Hu** (ANNA-1), anti-Tr, **anti-Ri** (ANNA-2), anti-mGluR1, anti-VGCC, anti-Ma1, anti-**CRMP5** (CV2), anti-Zic4, anti-VKCC, anti-mGLuR1	Shams'ili (2003), Peterson (1992), Hammack (1992), Clouston (1992), Darnell (2006), Clouston (1992), Sillevis (2000)
Opsoclonus-myoclonus	Neuroblastoma, SCLC, breast	**Anti-Ri** (ANNA-2), **anti-Yo** (PCA-1), **anti-Hu**(ANNA-1), anti-Ma1, **anti-Ma2** (Ta), **anti-amphiphysin**, **anti-CRMP5** (CV2)	Wong (2007), Bataller (2001), Dranell (2006), Luque (1991)
Retinopathies	SCLC, melanoma, breast	**Anti-recoverin**, anti-enolase, anti-TULP1, anti-PTB-like protein, anti-photoreceptor cell-specific nuclear receptor, **anti-CRMP5** (CV2)	Adamus (2004), Kikuchi (2000), Tateiwa (2001), Eichen (2001), Cross (2003)
Stiff person syndrome	Breast cancer, SCLC, Hodgkin's disease	**Anti-amphiphysin**, anti-GAD, **anti-Ri** (ANNA-2), anti-gephyrin	Lockman (2007), Pittock (2005), McCabe (2004), Butler (2000)

CRMP collapsin response mediator protein, *ANNA* antineuronal nuclear antibody, *PCA* Purkinje cell autoantibody, *VGKC* voltage-gated potassium channel, *NMDA N*-methyl-D-aspartate, *GABA* γ-aminobutyric acid-B, *AMPA* alpha-amino-3-hydroxy-5-methyl-4-isoxazoleprionic acid, *VGCC* voltage-gated calcium channel, *mGLuR1* metabotropic glutamate receptor type 1, *TULP1* tubby-like protein 1, *PTB* polypyrimidine-tract binding, *GAD* glutamic acid decarboxylase. Well-characterized onconeural antibodies are in bold

historically discussed in the context of PNS of the CNS. A number of these are discussed below.

Limbic Encephalitis

Paraneoplastic limbic encephalitis (PLE), first named 40 years ago, represents an inflammatory process affecting the mesial temporal lobes and limbic mesial cortical structures. PLE will usually present rapidly, within days to weeks. Patients typically present with memory loss, confusion, psychiatric abnormalities, and seizures. The initial personality changes and psychiatric manifestations including hallucinations, agitation, anxiety, and depression may lead to a presumptive diagnosis requiring admission to a psychiatric hospital, before the development of seizures and altered consciousness spur further evaluation.

The discovery of onconeural antibodies aids in diagnosis, although up to 10 % of patients with PLE will be seronegative or express uncharacterized antibodies (Graus et al. 2008). Eighty percent of patients have MRI T2-weighted and FLAIR hyperintensity in the bilateral mesial temporal lobes, although these areas rarely demonstrate gadolinium (GAD) enhancement. Focal or generalized slowing, and epileptiform activity, maximal in the temporal lobes, is seen on electroencephalography (EEG) in all (Lawn et al. 2003). CSF examination frequently shows

signs of inflammation with elevated protein, lymphocytic pleocytosis, and oligoclonal banding.

Small-cell lung cancer is associated with PLE in 50–60 % of patients, followed by testicular germ cell tumors (20 %) and breast cancer (8 %) (Gultekin et al. 2000). Other cancers associated with PLE include thymoma, ovarian teratoma, non-SCLC, and Hodgkin's disease (Table 1).

Limbic encephalitis (LE) has come to be characterized based on the location of target antigens, being either intracellular or neuronal cell surface receptors (Rosenfeld et al. 2010). Anti-Hu and anti-Ma2 are the most commonly discovered onconeural antibodies to intracellular antigens in LE. Anti-Hu, seen in up to 60 % of cases where antibodies are present, is the most common intracellular paraneoplastic antibody and, when positive in limbic encephalitis, denotes a 94 % correlation with underlying SCLC (Gultekin et al. 2000). Many patients with anti-Hu-associated PLE will have involvement in other areas of the nervous system, such as a subacute sensory neuronopathy (SSN). Anti-Hu antibodies, also frequently found in patients with SCLC without PLE, though in much lower titers, are associated with an intranuclear RNA-binding protein which functions in cell cycle regulation (Dalmau et al. 1990). Anti-Ma2 is a second intracellular antibody, primarily seen in young men who develop PLE in association with an underlying testicular germ cell tumor (Dalmau et al. 2004). They may have involvement outside the limbic system, including the hypothalamus, producing excessive daytime sleepiness, REM-sleep abnormalities, and hyperphagia. Treatment response is poor in these patients, as with other less frequently discovered intracellular antibodies, including anti-collapsin response mediator protein (CRMP) (CV2) and anti-amphiphysin (Tüzün et al. 2007). However, a dramatic response can be seen in anti-Ma2-associated PLE following immunotherapy and cancer treatment.

A more recently emerging discovery is limbic encephalitis associated with antibodies directed towards cell surface or synaptic proteins including the voltage-gated potassium channel (VGKC) (Vincent et al. 2004), the *N*-methyl-D-aspartate (NMDA) receptor (Irani et al. 2011), the γ-aminobutyric acid-B ($GABA_B$) (Boronat et al. 2011) receptor, and the alpha-amino-3-hydroxy-5-methyl-4-isoxazoleprionic acid (AMPA) receptor (Bataller et al. 2010). These newly discovered cell surface receptor antibodies may account for a majority of the patients with PLE and SCLC who were previously found to be seronegative for the well-characterized intracellular antibodies (Boronat et al. 2011). Unlike the well-characterized onconeural antibodies, these newly discovered antibodies, directed towards cell surface proteins, may in some cases be associated with an idiopathic or autoimmune neurological syndrome with no underlying malignancy. In addition, the antibodies are likely themselves pathogenic, and consequently, patients with these syndromes usually improve with immunotherapy aimed at removing antibodies form serum, such as IVIg and plasma exchange, as well as with treatment of the underlying tumor.

LE associated with VGKC antibodies is found to be paraneoplastic in about 30 % of cases, commonly occurring with SCLC and thymoma (Dalmau et al. 2008). A percentage of these patients may also develop a peripheral nerve hyperexcitability syndrome, such as neuromyotonia or Morvan's syndrome (neuromyotonia with CNS symptoms of hallucinations, delusions, and insomnia). NMDA receptor-associated LE is often described, in about 60 %, as occurring in a paraneoplastic form in young women with ovarian teratoma (Irani et al. 2011). In addition to the psychiatric symptoms and seizures common in PLE, these patients also have prominent dysautonomia, with labile heart rate and blood pressure, frequent hypoventilation, as well as a characteristic movement disorder with semi-repetitive orofacial and limb movements and dystonic posturing (Dalmau et al. 2008). Early and prominent seizures are a common presentation of LE associated with antibodies to the $GABA_B$ receptor. This syndrome is associated with SCLC in about

50 % of cases. $GABA_B$ receptor antibodies may be present, with glutamic acid decarboxylase (GAD) antibodies (Boronat et al. 2011). Anti-AMPA receptor encephalitis, usually seen in middle-age women, has an approximately 70 % association with an underlying tumor of the breast, lung, or thymus (Dalmau et al. 2010).

Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD), the first PNS to be recognized, is the best described and well documented and one of the most common paraneoplastic presentations of cancer. Sometimes preceded by a prodromal viral-like illness, cerebellar symptoms, including truncal and appendicular ataxia, nystagmus, and dysarthria, dominate the clinical picture. PCD may begin abruptly, progress over weeks to months, and then stabilize, usually leaving the patient significantly impaired, unable to walk or sit unassisted, and unable to perform fine motor tasks such as writing or eating. The degree and probability of severe impairment correlates somewhat with the underlying cancer and type of antineuronal antibody present.

As in PLE, there is usually evidence of inflammation in the CSF, though MRI usually does not demonstrate pathology until cerebellar atrophy develops late in the disease. MRI evidence of cerebellar swelling and enhancement of the cerebellar folia are reported by some (Darnell et al. 2006). During the early stages, fluorodeoxyglucose-PET may demonstrate cerebellar hypermetabolism, followed by evidence of hypometabolism in late stages (Dalmau et al. 2008). Histological findings, in the cerebellar cortex and deep cerebellar nuclei, include extensive loss of Purkinje cells with inflammatory infiltrates present at early stages of disease (Verschuuren et al. 1996).

Malignancies commonly associated with PCD include gynecologic cancers of the breast and ovary, SCLC, and Hodgkin's disease. Though not hard and fast, a correlation exists between certain paraneoplastic antibodies occurring in PCD and certain clinical features and cancer types. Breast or gynecologic cancer is usually detected with anti-Yo positivity (Peterson et al. 1992). Present in 38 % of patients in whom antibodies are detected, anti-Yo is the most common antibody in PCD. It targets the cdr2 antigen, normally expressed on Purkinje cells in the cerebellum and aberrantly expressed in ovarian and breast cancers.

With anti-Yo PCD, cerebellar symptoms usually present in isolation, often leaving patients with significant long-term disability resulting from irreversible Purkinje cell destruction. Similar to other antibodies that target intracellular neuronal antigens, treatment response is poor, although aggressive cancer treatment and immunotherapy, if initiated early in the course of disease, may improve the possibility of success (Dalmau et al. 2008). There are a few case reports of IVIg, given at a dose of 2 g/kg divided over 2–5 days, resulting in neurological improvement in patients with PCD and detectable anti-Yo antibodies. However, this is the exception rather than the rule (Widdess-Walsh et al. 2003). Patients who improved were treated within 1 month of symptom onset and usually received concurrent cancer therapy. Treatment at 1–3 months resulted in stable disease, and treatment outside 3 months usually had a poor outcome (Widdess-Walsh et al. 2003). Anti-Hu antibodies with SCLC also herald a poor prognosis, and while the cerebellar symptoms may predominate, other symptoms coexist, suggesting a more diffuse encephalomyelitis.

Hodgkin's disease and anti-Tr antibodies are also commonly associated with PCD. While anti-Yo antibodies are found in older women with PCD, anti-Tr antibodies are more commonly present in young men, reflecting the demographics of the underlying tumor. Hodgkin's disease, in contrast to other tumors, usually precedes the diagnosis of PCD, possibly because B symptoms lead to earlier diagnosis (Hammack et al. 1992). Patients with anti-Tr antibodies have a better neurological prognosis than those with Yo or Hu antibodies.

PCD, as is the case in LE, may also occur in the setting of antibodies directed against cell

surface antigens. P/Q type voltage-gated calcium channel (VGCC) antibodies are associated with SCLC and Lambert-Eaton myasthenic syndrome (LEMS). PCD sometimes occurs in SCLC, with LEMS, and high titers of VGCC antibodies. These patients may not exhibit any other recognized anti-Purkinje cell autoantibody and may harbor VGCC antibodies without developing LEMS, suggesting a role in the pathogenesis of cerebellar dysfunction (Mason et al. 1997). However, in that study, treatment with immunotherapy, as opposed to other paraneoplastic syndromes associated with neuronal receptor antibodies, did not alter the course of PCD. There have also been reports of PCD in the setting of Hodgkin's disease and antibodies against a glutamate receptor, metabotropic glutamate receptor type 1 (mGLuR1) (Sillevis Smitt et al. 2000).

Other associated antibodies include anti-CRMP5 and anti-Zic4 with SCLC. In patients with encephalomyelitis and testicular cancer, the presence of anti-Ma1 and anti-Ma2 antibodies correlated with development of cerebellar dysfunction (Darnell 2004).

Opsoclonus-Myoclonus

Opsoclonus-myoclonus (OM) syndrome comprises myoclonic jerks of the limbs and trunk, with opsoclonus, involuntary, arrhythmic, high-amplitude, and multidirectional saccades of the eyes. Opsoclonus may be constant, even during sleep, and may cause oscillopsia or blurring and oscillation of vision. OM is often associated with cerebellar ataxia, most often in children, and commonly referred to as opsoclonus-myoclonus-ataxia syndrome, though adult forms exist. Besides the classic triad of opsoclonus, myoclonus, and ataxia, pediatric patients in particular may exhibit sleep disturbance, cognitive dysfunction, and behavioral disruption. Neurological symptoms, especially in children, may resolve spontaneously or with treatment but may relapse. Brain MRI is usually normal but a mild CSF pleocytosis may be seen.

Pediatric OM etiology is diverse, including para- and post-infectious, toxic, and paraneoplastic causes. Pediatric OM is paraneoplastic in 40 % of patients, always associated with neuroblastoma. It is the most common pediatric paraneoplastic neurological syndrome in the medical literature, although it remains quite rare, occurring in 2–3 % of pediatric neuroblastoma (Rudnick et al. 2001). As the neurological symptoms in many cases of pediatric paraneoplastic OM respond well to immunotherapy, including IVIg, corticosteroids, and adrenocorticotropic hormone (ACTH), there does not appear to be permanent neuronal degeneration. More likely, transient antibody-mediated dysfunction occurs (Wong 2007). Furthermore, despite normal CSF cell counts, there is B cell expansion, which has been proposed as a candidate biomarker for the disease (Gorman 2010). A recent study demonstrated clinical improvement and reduced CSF B cells with rituximab, an agent that targets B cells, supporting a B-cell-mediated process (Pranzatelli et al. 2006). However, it has been difficult to consistently isolate specific autoantibodies, although recently, antibodies to surface proteins in cerebellar granular neurons in OM have been reported, and these exhibit a cytotoxic effect on neuroblastoma cells (Blaes et al. 2005). This antitumor immune response may explain the favorable prognosis for survival in children with coincident OM and neuroblastoma.

Among adults, paraneoplastic OM and anti-Ri antibodies are associated, usually in women with underlying breast cancer (Pittock et al. 2003). The Ri antibody recognizes the RNA-binding protein, Nova, which is strictly neuron specific and may regulate neuronal RNA metabolism (Musunuru et al. 2010). OM is also seen in patients with SCLC but predominately without the identification of a paraneoplastic antibody. However, anti-Hu and anti-amphiphysin are documented (Bataller et al. 2001). In contrast to children, adult paraneoplastic OM does not respond well to immunotherapy. Partial or complete neurological recovery may be seen with treatment of the underlying tumor (Bataller et al. 2001).

Retinopathies

PNS affecting the visual system predominantly involve the retina and optic nerve. Three distinct paraneoplastic visual syndromes are recognized: cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and paraneoplastic optic neuropathy (PON) (Damek 2005).

Patients with CAR often describe progressive, painless visual loss, over weeks to months, with photosensitivity, peripheral and ring scotomata, and flickering, light-induced glare. Clinically, evidence of cone- and rod-mediated abnormalities are seen on electroretinogram, and while initially normal, fundoscopic exam may demonstrate arteriolar narrowing (Damek 2005). Several antiretinal antibodies are associated with CAR, the most common and well-characterized being anti-recoverin, usually associated with underlying SCLC (Bataller et al. 2004). Recoverin is found in photoreceptor cells, and is thought to modulate dark and light adaptation through a calcium-dependent mechanism. Pathogenesis appears to relate directly to the anti-recoverin antibody, as it induces retinal cell apoptotic death in vitro (Shiraga et al. 2002), and may be found in the aqueous humor of CAR patients (Ohguro et al. 2002). Anti-enolase, a second commonly encountered antibody, is, unlike anti-recoverin, found in non-paraneoplastic retinopathy as well (Adamus et al. 2004). Other target antigens include tubby-like protein, photoreceptor cell-specific nuclear receptor, and polypyrimidine-tract-binding protein-like protein. Treatment, comprising tumor resection and immune suppression, including high-dose steroids and alemtuzumab (Campath), a monoclonal protein directed against CD52, has shown to improve vision in CAR (Alabduljalil et al. 2007).

Symptom onset in MAR, unlike CAR, is usually abrupt and includes night blindness and flickering light phenomena, with normal visual acuity. MAR is almost exclusively associated with melanoma, except for a few reports of a MAR-like syndrome with colon cancer (Jacobson et al. 2001). MAR generally presents months to years after the diagnosis of cancer, usually in the setting of tumor progression. It is believed that MAR antibodies react with retinal bipolar cells, although the exact target antigen is unclear. Recently, mitofilin, a mitochondrial protein, and titin, a striated muscle protein, have been suggested as possible targets. Both are present in retina and tumor cells, and antibodies are seen only in patients with melanoma and MAR (Pföhler et al. 2006). Response to immunosuppressive treatment is usually poor.

Paraneoplastic optic neuropathy rarely occurs alone; it is usually associated with other neurological manifestations including cerebellar degeneration, sensory neuropathy, LEMS, or an encephalomyelopathy. Patients usually present with unilateral, painless, visual loss, progressing to involve both eyes, with spots and flashes before the eyes (Damek et al. 2005). Paraneoplastic optic neuropathy usually occurs in the presence of antibodies to collapsin response mediator protein-5 (CRMP5) in association with SCLC (Cross et al. 2003).

Stiff Person Syndrome

Stiff person syndrome (SPS) is characterized by the gradual onset of stiffness and rigidity, initially in axial muscles, and progressing to proximal limb muscles, primarily involving the legs. Continuously contracting antagonist muscles, described as rock-hard or board-like to palpation, produce a rigid posture, making ambulation difficult, resulting in frequent falls. This muscle rigidity is typically absent during sleep. Patients experience sudden, painful muscle spasms, usually precipitated by touch or involuntary movement, sudden loud noise, or emotional stress. Because of its unusual presentation, SPS was believed to be a functional disorder and many patients were labeled hysterical.

Diagnosis is based on the clinical picture and electromyography (EMG) findings of continuous motor unit activity in affected muscles, which is, however, indistinguishable from normal voluntary muscle contraction. MRI and CSF

examination is usually normal. Other clues to diagnosis include muscle contraction in response to electrical stimulation, termed spasmodic reflex myoclonus, and a dramatic response to diazepam in relieving the stiffness. Differential diagnosis includes tetanus, hyperekplexia, and myelopathy.

SPS has both a non-paraneoplastic and paraneoplastic variant, both autoimmune. Glutamic acid decarboxylase (GAD) antibodies, found in 80 % of SPS patients, are associated with the non-paraneoplastic variant, usually in patients with other autoimmune diseases, particularly diabetes mellitus type 1 (Solimena et al. 1988). GAD catalyzes the decarboxylation of L-glutamate to γ-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the brain and spinal cord. Paraneoplastic SPS, seen in 5 % of SPS patients (Alexopoulos et al. 2010), is clinically similar to the non-paraneoplastic form, though arm involvement may be more prominent. Amphiphysin antibodies are most commonly detected in paraneoplastic SPS, usually in breast cancer patients, although SCLC and Hodgkin's disease are also reported (Pittock et al. 2004). Case reports of other antibodies associated with SPS include anti-Ri in a patient with lung cancer (McCabe et al. 2004), anti-gephyrin in a patient with mediastinal cancer (Butler et al. 2000), and rare reports of anti-GAD acting as a paraneoplastic antibody (Schiff et al. 2006).

Symptom response to immunotherapy, and the recent discovery that passive transfer of anti-amphiphysin IgG from patients with SPS produced dose-dependent stiffness in rats, suggests a B-cell-mediated process and direct pathogenesis of the antibody. IVIg was effective in 2 placebo-controlled studies in treating the non-paraneoplastic form of SPS associated with anti-GAD antibodies (Dalakas et al. 2001). The evidence for IVIg in paraneoplastic SPS is less substantial, only demonstrated in a few case reports. However, given that both GAD and amphiphysin are part of the presynaptic GABA/glycine inhibitory synapse and likely have similar disease-causing mechanisms, it is reasonable to suspect IVIg, in combination with rigorous treatment of the underlying cancer, may be effective in paraneoplastic SPS as well and may reduce or eliminate the need for benzodiazepines, such as diazepam and clonazepam.

Cross-References

- ▶ Cancer and Dermatomyositis
- ▶ Cancer and Neuropathies
- ▶ Paraneoplastic Neurological Syndromes, Overview

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Cancer and Thrombosis

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Synonyms

Deep vein thrombosis; DVT; LMWH; Low molecular weight heparin; PE; Pulmonary embolism; SC; Subcutaneous; TF; Tissue factor; UFH; Unfractionated heparin; Vascular endothelial growth factor; VEGF; Venous thromboembolism; VTE

Definition

Thrombosis is defined as presence of a blood clot in a vein or an artery. If a part of the obstructing clot dissociates and travels in the blood stream, it is termed as "thromboembolism." Venous thromboembolism is one of the common causes of cancer-related morbidity.

Introduction

The relationship between cancer and venous thromboembolism (VTE) has been recognized for almost two centuries. Historically, the French physicians, Bouillaud and Trousseau, are credited with initially describing the relationship between VTE and cancer. Multiple studies have provided considerable evidence for a two-way clinical association between VTE and cancer. While the risk for arterial thrombosis may also be increased in the setting of cancer, this entry will focus on the relationship of malignancy and VTE.

VTE is a common cause of morbidity and mortality in patients with cancer. Patients with cancer are at 2–20-fold higher risk of VTE than patients without cancer, and on average, 15 % of patients develop deep vein thrombosis (DVT) or pulmonary embolism (PE) during the clinical course of their cancer (Chew et al. 2006). The MEGA (Multiple Environmental and Genetic Assessment) study clearly indicated that patients with cancer have an elevated risk for VTE, particularly during the first few months after diagnosis and in the presence of distant metastases (Blom et al. 2005). Conversely, the risk for the diagnosis of cancer seems elevated for at least 2 years after a first episode of idiopathic VTE (Murchison et al. 2004). The data from several large prospective observational and retrospective studies suggest that mortality rate was significantly and consistently greater among cancer patients who developed VTE as compared to patients who did not (Khorana et al. 2007).

Pathophysiology and Risk Factors for Thrombosis in Cancer

Hemostatic and Fibrinolytic Activation

The hemostatic system has been shown to be highly activated in most cancers. Even in the absence of clinical thrombosis, the majority of patients with cancer have increased levels of coagulation factors V, VIII, IX, and XI, as well as increased levels of markers of hemostatic activation (e.g., thrombin-antithrombin; prothrombin fragment 1,2; fibrinopeptide; and D-dimer) (Hoffman et al. 2001). In addition, patients with disseminated malignancies seem to have deficient activity of von Willebrand factor

(vWF)-cleaving protease (ADAMTS13), resulting in unusually large vWF multimers, a key adhesive protein involved in primary hemostasis (Oleksowicz et al. 1999). Many tumors have shown an abnormal expression of high levels of the procoagulant molecule tissue factor (TF) (Rickles and Brenner 2008) and may express an additional cysteine protease cancer procoagulant (Falanga and Gordon 1985). In addition to the expression of TF, tumor cells enhance coagulation by expressing proteins that regulate the fibrinolytic system, including plasminogen activators and plasminogen-activator receptor, leading to an imbalance of fibrinolysis. Acute promyelocytic leukemia is notorious for causing both coagulopathy and hypercoagulable states, with leukemic cells with TF on their cell surface driving the coagulation disarray.

Stasis

At the organism level, malignancy, its complications, and treatments often lead to debility in patients associated with increased rates of sedentary behavior and decreased mobility (Osborne et al. 2008). These directly lead to stasis within the veins of the lower extremities, the sites of most thrombus formation. Venous catheters also lead to local disturbance in blood flow, which is associated with increased rates of thrombosis at the sites of catheters commonly associated with malignancy (Aw et al. 2012). Solid tumors, and lymphomas with large mass effect, may compress vessels and lead directly to vascular stasis, increasing the risk of clotting distal to the obstruction. Most commonly this is seen in the SVC-syndrome associated with mediastinal lymphomas, germ cell tumors, and primary cancers of the thoracic organs. Abdominal and lower extremity veins may be affected by any large, intra-abdominal tumor. Renal cell tumors present a unique situation, as vascular invasion by the tumor itself occurs, occasionally with extension as far as through the right atrium and into the pulmonary vasculature. Differentiating thrombosis from tumor may be difficult in these situations. Hepatobiliary tumors are often associated with portal vein thrombosis, both in the setting of cirrhosis and from portal vein flow reversal.

Vascular Damage

The vasculature is also intimately linked to both the oncologic process and its associated hypercoagulable state. As tumors grow, new vessel growth is required to furnish oxygen and other nutrients, as well as to clear the metabolic waste associated with highly active tumor cells. Cancer therefore stimulates new vessel growth via release of factors such as VEGF, which recruit endothelial cells for new vessel growth (albeit relatively disorganized and ineffectual, leading to the hypoxic and acidic microenvironment found in most tumors beyond a certain size). The same inflammatory mediators that lead to activation of the hemostatic system also lead to widespread activation of the vascular endothelium, which itself becomes a nidus for propagation of the coagulation cascade and ultimately thrombogenesis.

Central catheters and chemotherapeutic agents (see below) are also associated with vascular damage (Bona 1999). The direct physical irritation of blood vessels by central catheters leads to endothelial damage and clot formation and may lead to morbidity and mortality (Aw et al. 2012). Indwelling catheters are associated with a 27–67 % incidence of catheter-associated DVT (Bona 1999; Verso and Agnelli 2003). Chemotherapeutic agents are distributed to the tissues of the body by the vasculature, and these toxic agents may lead to endothelial activation. Some chemotherapeutic agents also appear to directly activate other components of the blood vessels (Otten et al. 2004), as can be seen with cisplatin treatment and arterial events (Moore et al. 2011).

Inflammation and Host Response

The close interactions between the inflammatory/immune system and the hemostatic system are a large part of what underlies the hypercoagulability found and associated with malignancy. Inflammatory mediators are produced by the immune effector cells in response to malignancy as part of the mechanisms to control and eradicate the rogue cancer cells. The hemostatic and inflammatory systems are linked most closely at the start of the intrinsic coagulation cascade, where factor XII is converted to its active form

by multiple members of the inflammatory system, including kininogen. In this way, besides TF acting on the extrinsic pathway, the intrinsic pathway is also recruited to amplify the coagulation cascade and thereby exacerbate the prothrombotic state (Rickles and Brenner 2008). Tumor-infiltrating macrophages may lead to downstream production of TF, and cytokine response to tumor and/or therapy may increase thrombotic tendencies.

Inflammation is also associated with both chemotherapeutic treatment and the infections caused by the immune-compromised state associated with chemotherapeutic treatments. Indeed, some of the highest rates of thrombosis in cancer patients are found during periods of hospitalization when patients are both immobilized, and the immune system is mounting high levels of inflammatory responses (Esmon 2003).

Cancer therapy also increases the risk for VTE, including surgery, chemotherapy, anti-angiogenic therapy, and hormonal therapy. Oncologic surgery is associated with an increased rate of VTE compared to noncancer surgery (White et al. 2003; Clagett and Reisch 1988). Chemotherapy has been known to increase the risk of thrombosis for some time (Lee and Levine 1999; Levine et al. 1988). In a prospective, multicenter, observational study, the overall incidence of VTE in an ambulatory population starting new chemotherapy was 1.93 % with a median follow-up of 2.4 months. The rate of VTE observed in this study (0.8 % per month) was substantially in excess of the estimated rate of approximately 0.04 % per month for the entire cancer population (Blom et al. 2004). Similarly, anti-angiogenic therapies may have significant effects on VTE incidence (Nalluri et al. 2008). Hormonal therapy is also recognized to increase the risk for VTE (Lee and Levine 1999; Ehdaie et al. 2011).

Specific factors increasing the risk for VTE include cancer type (e.g., pancreatic cancer, brain cancer, lymphoma) and stage (Levitan et al. 1999; Blom et al. 2005). In addition to the histology and type of cancer, there are various other factors that contribute towards the development of VTE in the setting of malignancy. Such factors have been identified using data from population-based databases, registries, hospital records, retrospective cohorts, prospective observational studies, and clinical trials (Table 1).

Cancer and Thrombosis, Table 1 Risk factors and biomarkers

Risk factors and biomarkers for development of VTE in cancer patients	Selected references
Extent of disease and metastasis	Levitan et al. (1999), Blom et al. (2005)
Chemotherapy	Blom et al. (2004), Lee and Levine (1999), Levine et al. (1988)
Hormonal therapy	Lee and Levine (1999), Ehdaie et al. (2011)
Anti-angiogenic therapy	Nalluri et al. (2008)
Central venous catheters	Aw et al. (2012), Verso and Agnelli (2003)
Thrombocytosis	Khorana et al. (2008)
Leukocytosis	Khorana et al. (2008)
Anemia	Khorana et al. (2008)
High levels of tissue factor (TF) expression or elevated levels of circulating TF	Belting et al. (2005)
Elevated soluble P-selectin level	Ay et al. (2008)
Histology of cancer	Levitan et al. (1999)
D-dimer	Ay et al. (2009)
Thrombin-antithrombin complex	Kakkar et al. (1995)
Microparticles (derived from platelets, megakaryocytes, or leukocytes)	Campello et al. (2011)
Erythropoiesis-stimulating agents	Bennett et al. (2008)
Surgery	White et al. (2003), Clagett and Reisch (1988)

Although the development of VTE in a patient with known cancer is the most common presentation, in some patients VTE may precede the diagnosis of malignancy (Murchison et al. 2004). Both retrospective and prospective studies have identified this phenomenon (Nordstrom et al. 1994; Sorensen et al. 1998). The variation in clinical presentation is likely due to the heterogeneous biology of different tumor types and reflects the limitations of detection or available diagnostic methods. Accumulating evidence now

suggests that oncogenic events also trigger activation of the coagulation cascade, leading to a thrombotic environment that not only manifests as VTE but also promotes the growth of the malignancy (Rickles and Brenner 2008).

Clinical Risk Stratification

It is increasingly recognized that ambulatory patients (especially those receiving systemic therapy) are at increased risk for VTE, and the vast majority of patients with cancer are in the ambulatory setting. The five-item Khorana model has been validated, using data from the Vienna Cancer and Thrombosis Study in a much broader range of patients (Khorana et al. 2008). The major advantage of this model is the easy availability of these common clinical markers, while the major limitation is the generalizability of the results. This model identifies about 7 % of cancer patients receiving chemotherapy in the ambulatory setting as high risk of VTE. Furthermore, the model is able to identify about 30 % of patients as low risk for VTE. This model is also being tested in an ongoing study, funded by the National Heart, Lung, and Blood Institute (www.clinicaltrials.gov NCT00876915).

Treatment and Secondary Prophylaxis of VTE in Cancer

Venous thromboembolic disease is a leading cause of death among cancer patients (Khorana et al. 2007). In addition, patients with cancer and thrombosis are at increased risk of VTE recurrence compared with noncancer patients and at increased risk of death due to malignancy compared to cancer patients without VTE (Levitan et al. 1999; Sorensen et al. 2000).

The recommended treatment for cancer-associated thrombosis is low molecular weight heparin (LMWH). For the initial treatment phase, post hoc data from randomized trials suggest comparable efficacy between unfractionated heparin (UFH) and LMWH. Based upon several prospective studies (see Table 2), recommendations for the treatment of proximal lower extremity DVT and/or pulmonary embolism in the setting of active cancer are with the use of extended LMWH therapy (Lyman et al. 2007; Geerts et al. 2008), and this therapy appears to be feasible. Some of the new anticoagulants including dabigatran and rivaroxaban are comparable to warfarin in efficacy and safety in a general patient population, but these trials include only a minority of cancer patients and have not been compared directly with LMWH.

Primary Prophylaxis

Primary anticoagulant prophylaxis is recommended in all oncology patients admitted to the hospital for surgical or medical reasons (Lyman et al. 2007). Although there are data for UFH, low molecular weight heparin (LMWH), fondaparinux, and warfarin for primary prophylaxis, contemporary studies have largely studied LMWH (Geerts et al. 2008). The ACCP, ASCO, NCCN, and ESMO guidelines recommend antithrombotic prophylaxis for cancer surgery for at least 7–10 days postoperatively (Lyman et al. 2007; Geerts et al. 2008). The benefit of extended prophylaxis for VTE following cancer surgery was first demonstrated by the ENOXACAN II study (ENOXACAN study group 1997). The role of antithrombotic prophylaxis in the prevention of central venous catheter-related thrombosis is controversial, and the international guidelines do not recommend prophylaxis for this indication (Lyman et al. 2007; Geerts et al. 2008).

The benefit of antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy has been evaluated in several studies that have demonstrated efficacy. An early high-quality study utilized low-dose warfarin to decrease VTE in women receiving therapy for breast cancer (Levine et al. 1994). More recently, prophylactic treatment with LMWH in

Cancer and Thrombosis, Table 2 Clinical trials for long-term use of LMWH in patients with VTE and cancer

Study	Trial design	Arms	Results	Comments
CANTHANOX (Meyer et al. 2002)	Randomized open label multi-institutional study	1. Enoxaparin	For enoxaparin group: 8 (11.3 %) had PE, 19 (26.8 %) had DVT, and 44 (62 %) had both DVT/PE	No statistically significant difference in combined primary outcome between enoxaparin group (7/67, 10.5 %) and warfarin group (15/71, 21.1 %, p = 0.09). Use of long-term LMWH in cancer patients was found to be more effective and safe
		2. Warfarin	For warfarin group: 11 (14.7 %) had PE, 25 (33.3 %) had DVT, and 39 (52 %) had both	
ONCENOX (Deitcher et al. 2006)	Randomized open label multi-institutional trial	1. Enoxaparin 1 mg/kg SC 2 times/day for 5 days, followed by 1 mg/kg SC 1 time/day for 175 days	Regarding primary outcomes, compliance rates were 97.9 % and 97 % for the two enoxaparin groups, and 90.1 % for warfarin group	Treatment with enoxaparin was feasible, generally well tolerated, and effective for a 180-day period in secondary prevention of VTE in cancer patients
		2. Enoxaparin 1 mg/kg SC 2 times/day for 5 days, followed by 1.5 mg/kg SC 1 time/day for 175 days	Secondary results for efficacy showed no difference in recurrent VTE rates for enoxaparin 1 mg/kg SC once daily group (1/29, 3.4 %), enoxaparin 1.5 mg/kg SC once daily group (1/32, 3.1 %), or warfarin group (2/30, 6.7 %, no p-value)	
		3. Enoxaparin 1 mg/kg SC twice daily for at least 5 days, until they reached therapeutic INR. Warfarin was started on day two of treatment and continued until patients received 180 total days of anticoagulation		
CLOT (Lee et al. 2003)	Randomized multi-institutional study	1. Dalteparin + coumarin derivative	27/336 (8.0 %) patients in dalteparin group had recurrent VTE, compared to 53/336 (15.8 %) patients in oral anticoagulant group (hazard ratio, 0.48; p = 0.002)	Dalteparin was more effective than oral anticoagulant in reducing the risk of recurrent VTE, without increasing bleeding risk
		2. Dalteparin alone		
LITE (Hull et al. 2007)	Randomized open label multi-institutional study	1. Tinzaprin	Of 737 patients, 18/369 (4.8 %) receiving tinzaparin had recurrent VTE at 3 months compared with 21/368 (5.7 %) receiving Vitamin K antagonist	Tinzaparin is similar in effectiveness to the usual-care vitamin K antagonist treatment for preventing VTE in a broad population of patients
		2. Vitamin K antagonist		
Tinzaparin prospective study (Tagawa et al., 2010)	Single-arm dual-center prospective study including biomarkers	Tinzaparin for 6 (up to 12) months at investigator discretion	11.3 % recurrent VTE rate (including unsuspected VTE on staging imaging); 3 % major bleeding	Increase in D-dimer at 1 month was associated with recurrent VTE (p = 0.009)

Cancer and Thrombosis, Table 3 Clinical trials of prophylactic anticoagulation in cancer patients receiving chemotherapy

Trial name	Patient population	Treatment arms	No. of patients	Results	Comments
Levine et al. (1994)	Women with breast cancer receiving chemotherapy	1. Warfarin 2. Placebo	311	There were 6 DVT, 1 PE in placebo group and 1 PE in warfarin group, a relative risk reduction of about 85 % ($p = 0.031$). Bleeding occurred in 2 placebo recipients and 1 warfarin-treated patient	Very-low-dose warfarin is a safe and effective method for prevention of VTE in patients
PROTECHT (Agnelli et al. 2009)	Patients with lung, breast, gastrointestinal, ovarian, or head and neck cancer receiving chemotherapy	1. Nadroparin 2. Placebo	1,150	Incidence of symptomatic venous and arterial thromboembolic events in nadroparin arm was 2 % versus 3.9 % in placebo group	High rates of VTE in lung (8.8 %) and pancreatic cancer patients (5.9 %) suggest need for more trials in these groups
CONKO 004 (Riess et al. 2009)	Advanced pancreatic cancer patients receiving chemotherapy	1. Enoxaparin 2. Observation	312	Sixty-five percent relative risk reduction of symptomatic VTE following use of enoxaparin 5 % versus 14.5 % for observation group	No overall survival difference between two groups
FRAGEM (Maraveyas et al. 2012)	Advanced pancreatic cancer patients eligible to receive gemcitabine	1. Gemcitabine + Dalteparin 2. Gemcitabine alone	123	Incidence of all-type VTE during the entire follow-up was 12 % in dalteparin group versus 28 % in those receiving chemotherapy alone	No significant difference in survival or bleeding events
SAVE-ONCO (Agnelli et al. 2012)	Metastatic or locally advanced solid tumors who were beginning to receive a course of chemotherapy	1. Semuloparin 2. Placebo		Occurrence of VTE was 1.2 % in semuloparin group versus 3.4 % in placebo group; HR 0.36; 95 % CI 0.21–0.60	No significant survival benefit found at 1-year follow-up

ambulatory patients receiving chemotherapy has been demonstrated to be efficacious with risk reductions VTE (see Table 3). However, it remains to be seen if these studies will change clinical practice, and no prospective studies have examined cost-effectiveness. Currently, VTE prophylaxis in ambulatory patients is recommended only for patients with multiple myeloma receiving thalidomide or lenalidomide-based combination chemotherapy (Lyman et al. 2007).

While not the subject of this entry, anticoagulants may have anticancer properties. Several retrospective studies pointing towards a survival benefit independent of VTE incidence led to a number of prospective studies with response or survival endpoints. Overall, pooled data point towards a reduction in the risk of death in subjects receiving anticoagulation therapy (Akl et al. 2007, 2010).

Conclusion

Venous thromboembolism is a significant source of morbidity and mortality in patients with cancer. Tumor factors, host factors, and treatment lead to the increased risk of VTE in the setting of

malignancy. Patients with cancer and thrombosis should be viewed as a special population and treated differently than similar patients with thrombosis in the absence of malignancy. The onset of idiopathic VTE may be the first manifestation of malignancy. In high-risk settings particularly, such as hospitalized and perioperative situations, VTE prophylaxis is indicated. Primary VTE prophylaxis in the ambulatory setting decreases the incidence of thrombosis, though the cost-effectiveness of this approach has not yet been demonstrated. Lastly, in addition to decreasing the risk of onset or recurrence of VTE, anticoagulants (in particular LMWH) may have antitumor properties which may lead to prolonged survival in the setting of malignancy.

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CD40

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Synonyms

BP50; CDW40; P50; TNFR superfamily member 5 (*TNFR5*)

Definition

Historical Background

CD40 is a type I integral membrane protein and a member of the tumor necrosis factor receptor (TNFR) family of molecules that functions as a major communication link between antigen-presenting cells (APCs) (B cells, macrophage, and dendritic cells (DCs)) and CD4 T cells. In the years prior to the discovery of CD40, there was widespread appreciation that antigen-specific activation of naïve B cells required contact-dependent interactions with activated T cells. However, only subsequent to demonstrating that contact was independent of cognate MHC interactions did it become clear that B-T cell contact required interactions with membrane-associated factors and not just cytokines (Banchereau et al. 1994; Lederman et al. 1993). CD40 was initially discovered as a B cell surface protein that could drive the proliferation and enhance the differentiation of B cells following stimulation with anti-CD40 antibodies (van Kooten and Banchereau 2000). CD40 expression occurred at all stages of B cell development (except for late-stage plasmablasts), whereas its ligand known as CD154 or CD40L was transiently expressed primarily on activated CD4 T cells. The absolute requirement for CD40-CD40L signaling in humoral immunity was first demonstrated in patients expressing a severe form of immunodeficiency termed X-linked hyper-IgM syndrome (HIGM1). These individuals displayed deficient CD40L expression, which resulted in significantly increased levels of IgM with a corresponding lack of "switched" isotypes (IgG, IgA, or IgE). Also, patients failed to form germinal centers (GCs) in their lymph nodes in response to antigenic challenge. Further work with animal models lacking either functional CD40 or CD40L confirmed that CD40 signals were essential for establishing both humoral and cell-mediated immune responses (Lougaris et al. 2005).

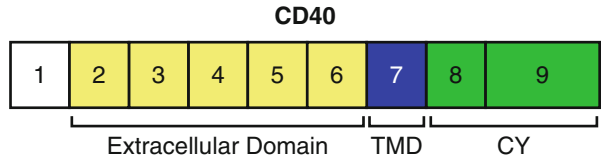
Structure of CD40 and CD40L

The structure of human CD40 was deduced from a cDNA isolated from a B cell expression library and shown to be a type I integral membrane protein comprised of 277 amino acids with a 193-amino-acid extracellular domain and a 62-amino-acid intracellular tail (Fig. 1) (van Kooten and Banchereau 2000). A comparison of the human and mouse forms of the protein uncovered a high level of identity at the amino acid level 62 % and complete conservation of 32 amino acids at the carboxyl terminal end of the protein. Also, all four of the extracellular cysteine residues are highly conserved, suggesting that the folding of the structural regions between mouse and human CD40 are identical. The mouse CD40 gene is located on the distal region of chromosome 2, which is syntenic to human chromosome 20Q11–Q13, harboring the human CD40 gene. CD40 exists as multiple spliced isoforms, and these different forms are correlated with distinct functional responses (Tone et al. 2001).

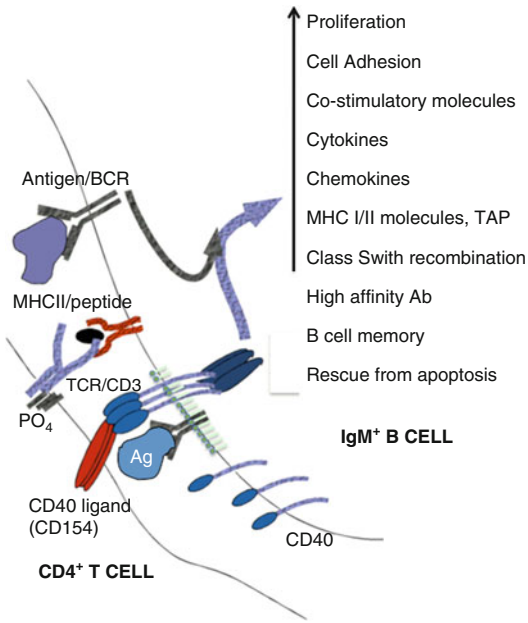
The structure of the CD40L protein was initially identified as a 33–39 kDa type II integral membrane protein that shared a high degree of homology to TNF-α. X-ray crystallographic data structure consisting of a sandwich of two β-sheets with jellyroll topology and revealed a surface topography that was homotrimeric with three-way symmetry. This type of 3-dimensional organization was reminiscent of both TNF-α and LT-α proteins. In addition to the full-length protein, two shorter, soluble versions of the CD40L protein were identified (31 and 18 kDa), and these forms retained their ability to trimerize and deliver biological signals through engaging CD40 (van Kooten and Banchereau 2000).

CD40 and B Cell Function

The initial discovery of CD40 was followed by an intense and productive period of investigation by many laboratories that focused primarily on the characterization of CD40-mediated functional responses in B cells. In vitro experiments revealed that CD40 was required for multiple B cell processes including proliferation, differentiation, and Ig production of both immature and mature B cell subsets (Banchereau et al. 1994; Noelle 1995; van Kooten and Banchereau 2000). In addition, early studies highlighted the critical



CD40, Fig. 1 Molecular organization of human CD40. Exons (1–9) are indicated by *boxes* and depicted as components of the extracellular domain, transmembrane domain (*TMD*), or cytoplasmic domain (*CY*)

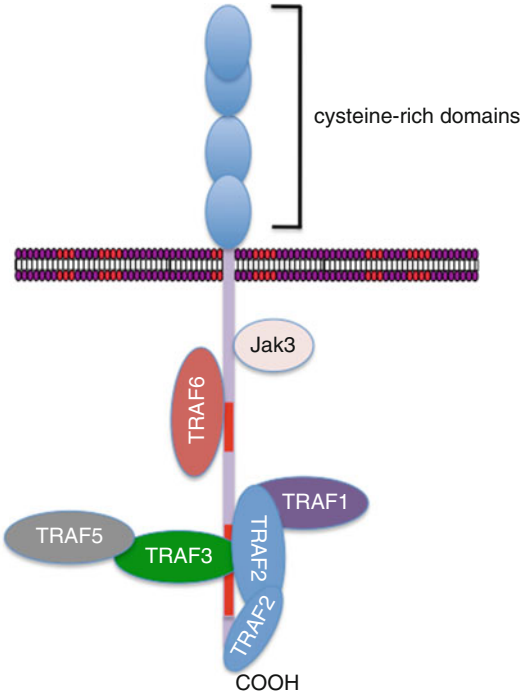


CD40, Fig. 2 CD40 signaling is provided to B cells that have encountered antigen (*Ag*) through the B cell receptor (*BCR*). These signals lead to a multitude of phenotypic changes that form the basis of the humoral immune response

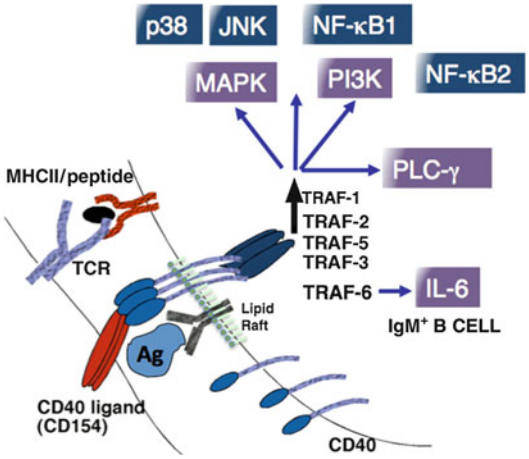
role of CD40 in the B cell maturation program including rescue from apoptosis, GC formation, isotype switching, somatic hypermutation, and B cell selection and development into memory cells. CD40 signals also directly affected cytokine production and expression of adhesion molecules and costimulatory receptors and increased the expression of MHC class I, MHC class II, and TAP transporter molecules (Fig. 2) (van Kooten and Banchereau 2000). However, CD40 signaling was shown to be dispensable for thymus-independent (TI) antibody responses, as evidenced by the fact that responses mounted to TI antigens (TNP-LPS and TNP-Ficoll) were similar between CD40-deficient and wild-type mice (van Kooten and Banchereau 2000). Overall, these findings revealed that CD40 is essential for generating responses to thymus-dependent (TD) antigens, responses that inherently result in the development of B cell memory and the corresponding production of somatically mutated, high-affinity antibodies.

Signaling Through Tumor Necrosis Factor Receptor-Associated Factors (TRAFs)

CD40 is distributed randomly throughout the plasma membrane and upon CD40L engagement clusters into cholesterol- and glycolipid-rich microdomains (termed lipid rafts). These unique membrane structures consist of concentrated pools of signaling molecules and are sites of initiation of signaling pathways for many different receptors including the B cell Receptor (BCR) and the T cell (TCR) receptor (Bishop et al. 2007). CD40 lacks intrinsic signaling capability and therefore is dependent on TNFR-associated factor (TRAF) adapter proteins to transmit CD40-mediated signals. This family of molecules is composed of six members, designated TRAF1 through TRAF6, that function by binding to discrete sites within the conserved carboxyl domain of TNFR family members including CD40 (termed the TRAF domain). Mapping experiments revealed that TRAF1, TRAF2, and TRAF3 bind to overlapping sites within the distal end of the CD40 intracytoplasmic tail that contains the consensus sequence PxQxT. A second, noncanonical binding site for TRAF2 resides adjacent to the carboxyl terminus (Elgueta et al. 2009). In contrast, the TRAF6 consensus site lies in the membrane proximal domain of CD40 (Fig. 3). The TRAF2/3 consensus site is required for the induction of



CD40, Fig. 3 The cytoplasmic domain of CD40 has two major binding sites for TRAF molecules which are situated proximal (TRAF6) and distal (TRAF1, 2, 3, and 5) from the membrane. A second TRAF2 binding site has been identified at the carboxyl end of the protein.



CD40, Fig. 4 Schematic of signaling pathways and transcription factors activated in response to CD40-CD40L engagement

NFκB, mitogen-activated protein kinase (MAPK)-JNK and MAPK-p38 pathways; however, in B cells, TRAF2 is a strong positive regulator and TRAF3 is a negative regulator of the canonical and noncanonical (NF-κB) pathways (Bishop et al. 2007; Elgueta et al. 2009). Accordingly, loss of TRAF3 is associated with an increased incidence of B cell lymphomas in both mice and humans (Bishop and Xie 2007). TRAF1 primarily binds to CD40 indirectly by forming multimers with TRAF2 and TRAF1 can bind directly to CD40 in the absence of TRAF2. TRAF5 does not directly bind to the CD40 tail but forms heterotrimers with TRAF3 upon CD40-CD40L contact. Lastly TRAF6 binding is required for the production of IL-6 by B cells. The binding of TRAF molecules as homo- or heterotrimers or as higher-order oligomers most likely drives the diverse array of downstream effector functions that are the consequence of CD40 signaling.

The engagement of TRAF signaling by CD40 results in the activation of multiple signaling cascades including the MAPK JNK and -p38 phosphoinositide 3-kinase (PI3K), and the phospholipase Cγ (PLCγ) pathways, leading to the induction of multiple signaling pathways including the canonical and noncanonical NF-κB-signaling pathways (Fig. 4). More recent findings suggest that TRAF-independent signaling may occur through the direct binding of Janus family kinase 3 (Jak3) to a consensus site within the intracytoplasmic domain of CD40. Binding of Jak3 induces the phosphorylation of signal transducer and activator of transcription 5 (STAT5). Together, these complex pathways transmit the essential transcription-dependent and transcription-independent signals that underlie CD40-specific functions (Bishop et al. 2007; Elgueta et al. 2009). Numerous studies suggest that the strength and duration of CD40 signals are critical for inducing specific downstream responses. This is observed at the level of different stimuli where anti-CD40 antibodies trigger only a subset of responses compared to trimeric CD40L (Bishop et al. 2007; Elgueta et al. 2009). For example, aggregating CD40 through binding to membrane-bound or trimeric CD40L is required for TRAF6 binding which results in the production of IL-6.

CD40 and the GC Response

It has been recently appreciated that the strength and duration of CD40 signaling have a major impact on the fate of antigen-selected B cells in secondary lymphoid tissues. B cells require CD40 signals to generate GCs as evidenced by the fact that an absence of signal fails to give rise to GC formation. The quality of CD40 signaling markedly influences the differentiation outcome of B cells in the GC such that when a high level of stimulus is provided in the context of an ongoing immune response, B cells are selected to differentiate into plasmablasts and are precluded from entering the GC reaction. However, once B cells are selected to colonize the B cell follicles and initiate GC formation, daughter centrocytes with enhanced BCR affinity for antigen will engage CD40L on follicular T helper cells, resulting in an effective block in Fas-dependent apoptosis through Bcl-XL- and c-FLIP-dependent mechanisms. In contrast, if a B cell expresses a BCR with weak antigen affinity, it fails to receive adequate BCR and CD40 survival signals and is deleted from the repertoire (Benson et al. 2007). The effects of graded levels of CD40 signals have been analyzed for affects in other APCs. Accordingly, strong and weak CD40 signals resulted in phenotypic and functional changes in both macrophage and DCs (Benson et al. 2007).

Expression of CD40 in Other Cell Types

Although early work focused on the critical role of CD40 in B cell biology, it became increasingly clear that CD40 was expressed in a much broader context and by a number of distinct cell types including myeloid cells, DCs, follicular DCs, endothelial cells, fibroblasts, epithelial cells, and keratinocytes (Elgueta et al. 2009; van Kooten and Banchereau 2000). Also, the spectrum of cells expressing CD40L was expanded to include mast cells, basophils, eosinophils, and activated platelets (Elgueta et al. 2009). Thus, the scope of effector functions that were controlled by CD40-CD40L signaling was greatly elaborated to more accurately reflect the expression pattern of these two molecules. Importantly, CD40-CD40L interactions were found to be critical for effective macrophage and DC function and to strongly influence T cell priming and consequently, T cell-mediated functions. The critical role of the receptor-ligand pair in APC function reflects the fact that CD40 signaling directly results in the upregulation of costimulatory molecules CD80 and CD86 on APCs. Ligation of these proteins by CD28 expressed on T cells leads to the induction of effector functions such as CD8 cytotoxic activity and the expression of multiple cytokines and chemokines critical for inflammatory responses (van Kooten and Banchereau 2000). Thus, in addition to roles in humoral immunity, CD40 and CD40L are central players in inflammatory processes and the cell-mediated immune responses to infection (Elgueta et al. 2009; Grewal and Flavell 1997; van Kooten and Banchereau 2000).

CD40 Expression and Macrophage Function

The interpretation of CD40 signals by macrophage and monocytes is known to be highly dependent on the tissue source of cells and most likely reflects the priming effect of the tissue environment (Elgueta et al. 2009). Generally, CD40 ligation of on macrophage/monocytes produce a proinflammatory signature including the production of cytokines (IL-1α and IL-1β, TNF-α, IL-6, and IL-12) and chemokines (MCP-1, RANTES, MIP-1α, and MIP-1β) and the upregulation of MHC class II and costimulatory molecules (CD80 and CD86) (Elgueta et al. 2009). Importantly, CD40 engagement also induces the expression of matrix metalloproteinases and nitric oxide (NO), mediators required for the destruction of damaged or infected cells. Interestingly, treatment of tumor-bearing mice with an agonistic anti-CD40 mAb was found to activate macrophage cytostatic activity, which led to the suppression of tumor cell growth (Loskog and Totterman 2007). Whereas TGF-β, a cytokine that inhibits CD40 responses and is expressed by many different tumor types, is capable of rendering tumor-associated macrophage incapable of mounting an attack on the tumor. Thus, the tissue environment and the nature of the delivery of the CD40 stimulus dictate the cellular outcomes that either can be protective from disease or contribute to disease progression.

The Role of CD40 in Infection

As mentioned earlier, CD40-CD40L interactions are critical for the development of CD8 T cell immunity, which in turn mediates immune responses to intracellular pathogens and tumors. Optimal activation of CD8 T cells requires engagement of the Ag receptor (TCR by Ag/MHC class I) and costimulatory signals through CD80/86 and CD28. In addition, some CD8 T cell responses require additional signals from CD4 T cells and/or dendritic cells. It is thought that CD4 T cells provide signals to dendritic cells via CD40L-CD40 interactions to prime and form CTL memory. Another hypothesis is that CD4 cells stimulate CD8 T cells directly by binding to CD40 expressed on CD8 T cells (Grewal and Flavell 1998; Munroe, 2009). Both $CD40^{-/-}$ and $CD40L^{-/-}$ mice exhibit impaired *Chlamydia muridarum* infection clearance compared to WT mice, as well as increased susceptibility to *Leishmania* infection. Also, $CD40^{-/-}$ mice have increased susceptibility and mortality to West Nile virus infection. Accordingly, patients with HIGMI have increased susceptibility to *Toxoplasma gondii* infection and other opportunistic infections including *cryptosporidium*, *Pneumocystis carinii*, *mycobacteria*, and cytomegalovirus, underscoring the fact that cell-mediated immunity is jeopardized in these patients (Etzioni and Ochs 2004). Thus, CD40 signaling is required for effective pathogen clearance through the induction of an array of effector functions and at multiple stages of infection.

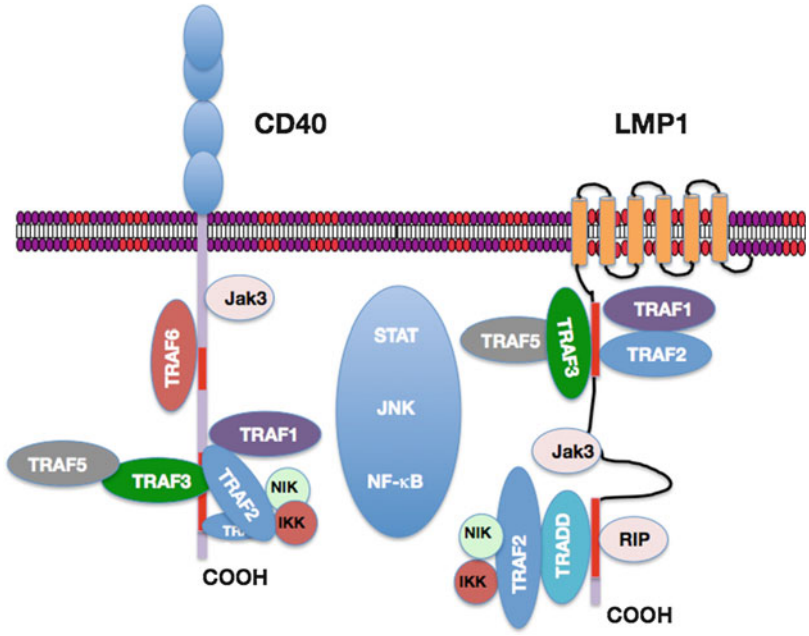
CD40 and Autoimmunity

The importance of CD40-CD40L interactions in mediating inflammatory responses formed the basis of investigating a possible role in autoimmune disorders. Not surprisingly, deregulated CD40-CD40L expression was found to be prominently featured in both systemic and tissue-specific autoimmunity (Peters et al. 2009). Importantly, anti-CD40L treatment was able to suppress autoantibody production in models of collagen-induced arthritis, systemic lupus erythematosus (SLE) nephritis, and experimental autoimmune encephalomyelitis (EAE). In addition, treatment of mice with anti-CD40L antibodies blocked the development of T cell-mediated disorders through interfering with the priming of self-recognizing T cells. In all cases, treatments were accompanied by a reduction in damage and/or infiltration of leukocytes to target tissues. Because many autoimmune disorders have a complex pathophysiology, the levels at which the blocking antibodies are acting are most likely highly variegated and include antigen presentation, antibody production, and induction of inflammatory cytokines (Peters et al. 2009). For both lupus nephritis and EAE, blocking antibodies interfered with ongoing disease, indicating that CD40-CD40L interactions are essential for the effector phase of disease.

In many autoimmune diseases, there is a significant increase in CD40 and/or CD40L expression; however, in most cases, heightened expression is not correlated with genetic polymorphisms at the respective loci. An exception to this observation is a CD40 polymorphism associated with the development of Graves' disease (GD). This disease leads to loss of thyroid gland function and is associated with autoantibodies against the thyroid-stimulating hormone receptor. In this particular case, linkage studies revealed that the CD40 gene locus was strongly linked with GD. This association is due to a C/T polymorphism in the Kozak consensus sequence that flanks the ATG start codon and is essential for translation initiation. Enhanced CD40 expression has been identified in thyroid tissue of GD patients bearing the C polymorphism and is thought to be a contributing factor to the pathogenesis of disease (Maier and Hafler 2009).

The Impact of CD40 on Atherosclerosis

Activated T cells and macrophages are important factors in the generation of inflammatory atherosclerotic plaques, and associated immune responses may, in some cases, constitute an autoimmune response against an unidentified antigen (Anand et al. 2003). Endothelial cells (EC), smooth muscle cells (SMC), and macrophage participate in atherogenesis (Anand et al. 2003). Importantly, human EC express CD40 and ligation through CD40L engagement leads to upregulation of adhesion molecules, which are



CD40, Fig. 5 A comparison of the intracellular domains of CD40 and LMP1 showing the approximate sites of TRAF binding as well as binding of Jak3, TRADD, RIP, NIK, and IKK. Listed within the *blue oval* are the pathways activated by those two molecules

also critical biomarkers of human atheromas. CD40 and CD40L are co-expressed on vascular endothelium and SMC in atherosclerotic lesions. Therefore, CD40L expressed by both the vascular wall and resident T cells is capable of ligating to CD40 expressed on EC, SMC, and infiltrating macrophage. This signaling cascade ultimately results in the expression of cytokines, matrix metalloproteinases, and adhesion molecules, all proteins normally present at high concentrations in human atheroma (Anand et al. 2003).

CD40 and Its Viral Mimic, LMP1

Epstein-Barr virus (EBV) is a γ-herpes virus that preferentially infects human B cells. Its successful persistence in cells is sustained by the function of several virally encoded proteins that are mimics of cellular factors critical for B cell physiology. The viral latent membrane protein 1 (LMP1) is one such protein and has been identified as the functional homologue of CD40 (Bishop and Hostager 2001). Important similarities exist between CD40 and LMP1 including the fact that signaling through either molecule leads to activation, proliferation, and survival of B cells. This functional identity reflects the ability of the intracellular domains of both LMP1 and CD40 to bind TRAF molecules and activate overlapping signaling pathways (Fig. 5). There are, however, recognized differences in the TRAF binding patterns of LMP1 and CD40 that suggest corresponding differences in select functional responses. Whereas both LMP1 and CD40 interact with TRAFs 1, 2, 3, and 5, only CD40 binds directly to TRAF6. Also, LMP1 requires TRAF3 as a positive regulator of NF-κB activity, whereas it is a negative regulator for the same pathways in B cells. Finally, LMP1 selectively binds to the tumor necrosis factor receptor-associated death domain (TRADD) protein and receptor-interacting protein (RIP) (Kilger et al. 1998).

Other distinctions in TRAF utilization directly reflect functional differences between CD40 and LMP1. As mentioned above, CD40L engagement with CD40 on B cells results in the association of CD40 with TRAF2/3 complexes; however, TRAF2 and 3 are rapidly ubiquitinated and degraded through the proteosome (Bishop et al. 2007). This degradation step leads to the downregulation of signal transmission. LMP1-mediated TRAF binding is highly stable and the difference in stability likely accounts for the fact that LMP1 provides a stronger and more

sustained signal than CD40. However, B cells that express both LMP1 and CD40 and receive signals through CD40-CD40L show an overall dampening of responses compared to LMP1 signaling alone. A plausible explanation for this lowered response is that selective TRAF degradation that accompanies CD40 signaling reduces the effective pool of TRAF3 available for subsequent signaling by LMP1. Another difference between CD40 and LMP1 is that LMP1 is constitutively located in the lipid rafts whereas CD40 moves into lipid rafts upon CD40L contact. Finally, the most striking difference between LMP1 and CD40 is that LMP1 constitutively signals in a ligand-independent manner through the self-aggregation of its 6 transmembrane-spanning domains and CD40 requires trimerization by binding to CD40L (Bishop and Hostager 2001).

To better define functional similarities of LMP1 and CD40 signaling, mice were created that expressed LMP1 in B cells deficient for CD40. Surprisingly, only a partial restoration of CD40 activity was achieved in inducing antibody class switching to IgG1, but not GC formation or the production of high-affinity antibodies after immunization. LMP1 expression even blocked GC formation in the presence of the endogenous CD40 receptor, indicating that LMP1 had an overall negative effect on differentiation. Also, constitutively active CD40 signaling in B cells produced by a fusion protein of the transmembrane domain of LMP1 and the signaling domain of CD40 inhibited the GC reaction, suggesting that GC formation can be blocked by the constitutive activation of B cells by either LMP1 or CD40 (Bishop et al. 2007).

CD40 and Cancer

The discovery that the CD40 pathway was absolutely critical for promoting B cell proliferation and rescue from apoptosis led to experiments that tested the role of CD40 in tumorigenesis. CD40 overexpression occurs in the vast majority of hematopoietic cancers and in greater than 75 % of all epithelial cancers. Also, in many cases, CD40 and CD40L are co-expressed on the same tumor cell. Accordingly, several hematopoietic cancers, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Burkitt lymphoma, enhance proliferation and survival through an autocrine CD40-CD40L loop that acts primarily through the constitutive activation of NF-κB (Bereznaya and Chekhun 2007). This type of process may also be active in solid tumors that are capable of co-expressing CD40 and CD40L such as breast and kidney carcinoma and melanoma, where the presence of CD40L correlates with a more aggressive malignancy and shorter patient survival than tumors lacking CD40L (Bereznaya and Chekhun 2007). CD40 signaling can also drive tumor cell migration through the PI3K and NF-κB signaling pathways. It has been demonstrated that CD40 can indirectly promote tumor growth since chronically produced CD40L in the tumor microenvironment facilitates angiogenesis through the activation of CD40 expressed by endothelial cells. Metastasis can also be enhanced by tumor-expressing CD40 interacting with CD40L expressed on activated platelets (Bereznaya and Chekhun 2007).

It is clear that specific CD40-dependent signals are capable of providing growth and survival advantages to specific hematological malignancies; however, in a number of cases, CD40-CD40L interactions can also severely inhibit tumor growth. For example, a subset of aggressive B cell lymphomas respond to CD40 ligation with sensitization to apoptosis induced by chemotherapy, CD95/Fas engagement, or serum withdrawal. Also, CD40L treatment of primary high-grade B cell lymphoma, multiple myeloma, and Burkitt lymphoma results in a marked decrease in cell proliferation both in vitro and in xenotransplanted mouse models. Additionally, deregulation of the CD40 pathway has been shown to occur in CD4+ T cells from patients with chronic lymphocytic leukemia, and these leukemic cells are capable of suppressing CD40L expression in cocultured allogeneic T cells. In contrast, CD40 ligation of low-grade B cell malignancies, such as follicular lymphoma, chronic lymphocytic leukemia, and hairy cell leukemia, often stimulates cell

proliferation, underscoring the fact that the response to CD40 can be highly dependent on the differentiation state of the tumor.

The CD40 pathway is critical for the antitumor immune response through the function of DCs that are capable of cross-presenting tumor antigens to CD8 cytotoxic T cells and priming them for activation. Maturation of the DCs is required for effective priming, and this process is controlled by the binding of CD40 on the DCs with CD40L on CD4 T cells (Bereznaya and Chekhun 2007). Mature DCs have upregulated antigen-processing and presentation pathways and migrate to the lymph nodes to activate naïve CD4 and CD8 T cells. The requirement for CD40 in DC priming provides an explanation for the impaired tumor antigen-specific CTL activation in CD40-deficient mice. These findings confirm the requirement for CD40 in antitumor immunity and highlight the potential for this pathway being a viable target for cancer immunotherapy. Notably, multiple studies have addressed this and demonstrated that expression of CD40L in tumor cells or direct activation of DCs with anti-CD40 antibodies results in long-lasting systemic antitumor immune responses mediated by CD8 T cells.

Summary

CD40-CD40L interactions regulate the activation and the differentiation of a number of different cell types into effector cells. In particular, widespread expression of CD40 and CD40L has been demonstrated under pathological conditions, suggesting that this pathway is important for immune homeostasis and that deregulation leads to catastrophic consequences. Interference with CD40-CD40L interactions through the use of blocking antibodies reveals the potential of harnessing this receptor-ligand pair for the treatment of various autoimmune diseases and cancer. Finally, future work will more clearly elucidate the cross talk between the innate and adaptive immune responses and decipher how CD40-CD40L communication is moderated by signaling pathways initiated by viral infection and/or other types of immune challenges.

Cross-References

- ▶ Animal Models in Rheumatoid Arthritis
- ▶ B7 and CD28 Families
- ▶ Cytotoxic T Lymphocytes
- ▶ Immunodeficiency in Autoimmune Diseases
- ▶ Lymphocytes in Atherosclerosis
- ▶ NF-κB
- ▶ Therapeutic Considerations in Kidney Diseases Due to Glomerulonephritis
- ▶ Tumor-Infiltrating T Cells

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