CLINICAL VIGNETTE

Malignancy Presenting as Paraneoplastic Itch

Soleyman Rokhsar, MD

Case

A 59-year-old male with no significant past medical history presented for a routine annual visit. During the evaluation, he described having pruritus for 6 months. He had itching of his trunk and extremities on a daily basis, worse at night. He was not on any medications. He had tried changing his soap and shampoo without any change in his symptoms. Exam was unremarkable. There was no evidence of skin abnormalities. Complete blood count, creatinine, electrolytes, liver function tests, thyroid stimulating hormone, erythrocyte sedimentation rate, and C-reactive protein were normal. He was advised to keep a food diary, but this did not reveal the cause of his pruritus.

Several months later, the patient returned after having noticed lumps on his outer neck. Review of systems was negative, except for ongoing pruritus. Exam revealed lymphadenopathy in the left lower cervical and supraclavicular areas. The left tonsil was enlarged compared to the right but appeared normal otherwise. Neck CT revealed a left tonsillar mass with left sided necrotic lymphadenopathy. Biopsy of the tonsillar mass revealed classic Hodgkin's lymphoma. He underwent 4 months of chemotherapy with complete remission of his lymphoma and complete resolution of his pruritus.

Discussion

The International Forum on the Study of Itch (IFSI) classifies pruritus as chronic if it has lasted for more than 6 weeks. Chronic pruritus has many different etiologies. Causes can be categorized into three groups (Groups I-III) based on skin changes.[1] In the first group (Group I), pruritus occurs on skin that is primarily diseased and inflamed. This group includes primary dermatologic conditions, such as skin infections, atopic dermatitis ad psoriasis. This is the most common cause of chronic pruritus. In the second group (Group II), pruritus occurs on skin that is normal. This group includes systemic diseases, such as kidney and liver diseases, and malignancy. In the third group (Group III), pruritus occurs secondary to persistent scratching due to other issues. This group includes neurologic conditions, such as multiple sclerosis and post-herpetic neuralgia, and psychiatric conditions, such as schizophrenia.[1]

Paraneoplastic itch (PI) is one of the causes of chronic pruritus in Group II. PI is defined by IFSI as "systemic (not local) reaction to the presence of a tumor or a hematologic malignancy neither induced by the local presence of cancer cells nor by tumor therapy. It usually disappears with remission of the tumor cells and can return with its relapse."[2] PI has also been defined as "(i) itch that occurs early during the natural process or even precedes the clinical evidence of the malignancy, (ii) it is not caused by the neoplastic mass invasion or compression, and (iii) subsides after the removal of the tumor."[3]

Pruritus is a well-recognized symptom of malignancy. In one study of 700 patients with cancer, pruritus was reported in 5.85% of cases.[4] Pruritus associated with malignancy can be divided in two categories. One is pruritus related to a local reaction to tumor or pruritus related to treatment. The other is paraneoplastic itch. PI may precede the diagnosis of malignancy, as it did in the case presented here. There have been several recent studies that have tried to address this topic.

In a cohort study of 12,813 patients in Denmark, standardized incidence ratios (SIRs) were calculated for patients with pruritus who were later diagnosed with cancer. The SIRs reflected the observed cases of cancer to the expected cases based on national incidence rates. There was a 13% increase in the incidence of cancer among patients with chronic pruritus. The increase was 2.14-fold in the first 3 months of a diagnosis of pruritus. By the end of the first year, the increase fell to 1.42-fold. After 10 years of follow-up, the incidence was basically the same as the general population. Hematologic and solid cancers were both found at higher rates. Hodgkin's lymphoma, non-Hodgkin lymphoma, liver cancer and pancreatic cancer had confidence intervals that did not overlap 1.0 suggesting statistical significance.[5]

In a cohort study of patients in the United Kingdom, 8,744 patients with chronic pruritus and no skin findings (group II patients as defined by IFSI) were matched with 31,580 patients without chronic pruritus. The adjusted hazard ratio (HR) for overall malignancy was 1.14, but the confidence interval did not suggest statistical significance. However, the adjusted HRs for hematologic and bile duct malignancies were significant, with ratios of 2.02 and 3.73 respectively. The incidence of these malignancies was very low at 0.0016 per person-year for hematologic malignancies and 0.0003 per person-year for bile duct malignancies.[6]

A case-controlled study of these 8,744 patients was also done. The 398 patients with chronic pruritus and no skin findings who

eventually developed cancer were compared to the 8346 patients who did not develop cancer. Median time from chronic pruritus diagnosis to cancer diagnosis was 1.98 years (standard deviation 1.45). Potential predictors of malignancy development were age > 60 years, male gender, smoking (current or prior), liver disease, renal disease, diabetes, and current alcohol use. Of these predictors, only the first three were statistically significant.[7]

The first step in determining the cause of chronic pruritus is to perform a complete history and physical examination. Based on this clinical presentation, one can determine whether the pruritus is from a primary dermatologic condition or a secondary condition. Diagnosis of primary dermatologic conditions is usually straightforward. If the diagnosis it not clear from the clinical presentation, then a skin biopsy is often helpful in establishing the diagnosis. Diagnosis of secondary conditions causing chronic pruritus may require additional workup, including laboratory tests and radiologic exams.

Paraneoplastic itch is an etiology that should be on the differential for a patient presenting with chronic pruritus. Based on recent studies on PI, hematologic and bile duct malignancies should be considered as a cause, especially in men, those over age 60, and those with a smoking history. A work-up targeting these malignancies is reasonable if the diagnosis of chronic pruritus is unclear.

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