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CLINICAL VIGNETTE

Paraneoplastic Inflammatory Arthritis Associated with Pulmonary Adenosquamous Carcinoma

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Clinical Case

A 74-year-old woman with breast cancer and hypothyroidism was referred to rheumatology for evaluation of progressively worsening hand arthritis over six months. She reported onset of bilateral hand pain and swelling in the MCPs and PIPs about two weeks after she received a Covid-19 booster vaccination. She initially managed her hand pain and swelling with acetaminophen and added ibuprofen about 800mg twice daily. After about 4 months, she presented to her primary care physician for evaluation and management. She was diagnosed with osteoarthritis and referred to occupational therapy. However, her symptoms progressed and she developed what she called "curling" of all digits of both hands with worsening stiffness and swelling. She was referred to Rheumatology for further evaluation and management.

Initial evaluation in the rheumatology office, included additional history of Raynaud's Phenomenon over the last 6-12 months, as well as dry eyes and mouth. She started over the counter eye drops and increased her water intake. She also reported an unintentional 30-lb weight loss over the last 6 months, and onset of persistent dry cough approximately three months prior to presentation.

Her past medical history was significant for breast cancer, 15 years prior, managed with lumpectomy, chemoradiation, and anastrazole. She developed chemotherapy induced neuropathy. She also had hypothyroidism, stable on levothyroxine. She denied family history of breast cancers or autoimmune diseases and reported no alcohol or substance use. She was an active smoker for 45 pack a year history with one pack a day use at initial consultation.

Initial Physical Exam revealed temporal wasting, dry appearing oral mucosae, and diffuse wheezes across bilateral lung fields. Scant non-specific, urticarial appearing dermatitis with excoriations were present over bilateral biceps. There was bilateral trace lower extremity edema to the mid tibia. Musculoskeletal exam was significant for inability to abduct or flex shoulders beyond 90 degrees on active range of motion due to pain, and impressive swelling and warmth of all MCPs and PIPs on all the digits of both hands with flexion deformities at the MCPs and PIPs and inability of the patient to extend her fingers.

Serologic testing was consistent with Sjogren's Syndrome, including an ANA 1:1280 nuclear pattern, low titer Rheumatoid Factor, and positive SSA antibody. Extensive serologic testing for other connective tissue diseases including systemic lupus erythematosus, systemic sclerosis, and dermatomyositis was negative. An underlying malignancy was suspected given her significant smoking history, dry cough, weight loss and rapid onset of severe inflammatory arthritis not typical for Sjogren's Syndrome. CT of the chest revealed a large, irregular, spiculated mass in the left lower lobe consistent with a primary lung neoplasm. Bronchoscopy confirmed poorly differentiated adenosquamous carcinoma of the lung.

Discussion

Paraneoplastic rheumatology syndromes are an important clinical entity. The more common paraneoplastic syndromes seen in rheumatology include hypertrophic osteoarthropathy, RS3PE syndrome, palmar fasciitis and polyarthritis, tumor-induced osteomalacia, cancer-associated dermatomyositis, and, finally, paraneoplastic polyarthritis, which we have detailed. The pathogenesis of these syndromes is not well-understood. Underlying mechanisms for some of these processes are thought due to soluble factors released by tumor cells. In hypertrophic osteoarthropathy, digital clubbing and increased periosteal activity of tubular bones is hypothesized to be related to overproduction of Fibroblast growth factors (FGF), platelet derived growth factor, and vascular endothelial growth factor (VEGF). Elevated levels of VEGF have also been implicated in RS3PE, and elevated levels of FGF have been connected to renal phosphate wasting in tumor-induced osteomalacia. In cancer-associated dermatomyositis, it is thought that the anti-tumor immune responses induce autoantibodies that cross react with regenerating muscle tissues. There is less known about the mechanisms of palmar fasciitis and paraneoplastic polyarthritis.[1]

Paraneoplastic syndromes are difficult to diagnose, with the strongest argument for paraneoplastic symptoms is a close temporal relationship between the onset of symptoms and the diagnosis of the malignancy. Our patient experienced rapid onset of peripheral arthritis six months prior to discovery of her pulmonary malignancy. Her poor response to NSAID and oral

steroid therapy is characteristic of paraneoplastic polyarthritis. In paraneoplastic polyarthritis, the arthritic symptoms commonly improve when the underlying tumor is treated. It is yet to be seen whether treatment of the underlying tumor will result in improvement of her inflammatory arthritis symptoms. Other characteristic features of paraneoplastic polyarthritis are her advanced age, involvement of her hands and wrists, lack of erosive disease or other inflammatory changes on radiographs, and her underlying pulmonary malignancy, the most common solid tumor associated with paraneoplastic polyarthritis.[2,3]

In a recent multicenter retrospective review of 92 cases of paraneoplastic arthritis, lymphomas were the most common hematologic malignancies responsible for paraneoplastic polyarthritis.[4] With respect to solid malignancies, the most common tumor associated with paraneoplastic arthritis was pulmonary malignancy, with adenocarcinoma the most common subtype. Interestingly, there was a significant increase in anti-CCP antibody present in patients with paraneoplastic polyarthritis as compared to a healthy control group. Rheumatoid factor positivity was present in about 20% of patients with paraneoplastic polyarthritis, but this was not significantly different from healthy controls (12%). The study did not report for ANA or other autoantibody positivity. Other solid tumors associated with paraneoplastic arthritis included breast, pancreatic, gastric, bladder, and prostate. Knee, ankles, hands, and wrists were the most commonly impacted joints in paraneoplastic polyarthritis syndromes. The results of this review were relatively consistent with a review of 35 reports of paraneoplastic polyarthritis.[5] They reported pulmonary malignancies to be the most common solid tumor associated with paraneoplastic polyarthritis, with slightly greater than half of presentations occurring in males.

While paraneoplastic syndromes are rare, it is important to include them on the differential diagnosis, particularly if patients have risk factors for malignancy and have not had age appropriate cancer screening.

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