Paraneoplastic Syndromes Masquerading as an Autoimmune Disease

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Paraneoplastic syndromes are reported in 8–15% of patients diagnosed with cancer [1]. They are defined as syndromes that occur due to an underlying malignancy, which has yet to be diagnosed, or at the time of the diagnosis and less frequently following the diagnosis of a malignancy. Several mechanisms are involved including autocrine and paracrine mediators, hormones, peptides, cytotoxic lymphocytes, and cytokines [1,2].

There are different types of paraneoplastic syndromes. The most common are neurological and endocrine. Musculoskeletal and rheumatologic syndromes also exist. Lung tumors and thymomas are the most reported malignancies that are associated with paraneoplastic syndromes and can manifest before tumor diagnosis or after tumor resection [2].

Paraneoplastic rheumatological and autoimmune phenomena may occur through several mechanisms involving cytotoxic lymphocytes and cytokines [1,3]. The severity of the paraneoplastic autoimmune phenomena is directly correlated with the malignancy burden. When therapy is initiated for the malignancy, in most cases, the paraneoplastic manifestations subside [4].

Atypical manifestations of an autoimmune disease, such as development in the elderly or inadequate expected clinical and laboratory response to standard of care therapy, should raise suspicion of a possible underlying paraneoplastic autoimmune phenomena and prompt an early cancer detection attempt [5]. Some reported presentations include sudden onset asymmetrical polyarthritis, rheumatoid arthritis (RA) with monoclonal gammopathy, polymyalgia rheumatica unresponsive to prednisone therapy, new onset Raynaud's phenomenon, or cutaneous leukocytoclastic vasculitis over the age of 50 years [3]. We report four patients with paraneoplastic syndromes masquerading as autoimmune diseases who had unique manifestations.

PATIENT DESCRIPTION

CASE 1

A patient with a past medical history of hypertension, *Sjögren's* syndrome, and systemic lupus erythematosus (SLE) with neuropsychiatric involvement was treated with intravenous immunoglobulins (IVIG) and had been in remission for many years. The patient presented with a flare of SLE manifested by arthritis, pleuritic chest pain, pancytopenia, high antinuclear antibodies (ANA) titers, and low complement levels. The patient did not respond to standard care therapy. Belimumab (Benlysta) IV therapy was initiated. A few months later, the patient underwent a screening mammography that depicted a suspicious nodule and local lymphadenopathy. The nodule biopsy confirmed the diagnosis of a left breast infiltrating duct carcinoma. The patient underwent left lumpectomy and local left axillary lymphadenectomy and received hormonal therapy with lentrozole and local radiation therapy. The patient responded favorably with complete remission of SLE and malignancy. Two years later, the patient presented with a new SLE flare that manifested in a similar manner. A repeated mammography showed a suspicious nodule. A full-body computed tomography (CT) scan revealed bone and liver metastases. The final diagnosis based on a new breast nodule was breast cancer recurrence. This case illustrates exacerbations of a known autoimmune disease after a long period of remission in a patient who had paraneoplastic syndrome

heralding new onset and of recurrence of malignancy.

Table 1. Summary of case reports and findings

Case number	Autoimmune disease	Presentation	Malignancy	Outcome
1	SLE	Exacerbation	Breast	Good response to treatment
2	Cicatricial pemphigoid	Exacerbation	Lung	Death within 8 months
3	Scleroderma	Atypical	Lung	Good response to treatment
4	ASIA syndrome	Persistent, moderate response to IVIG therapy	Thyroid	Workup

ASIA = autoimmune/inflammatory syndrome induced by adjuvants, IVIG = intravenous immunoglobulins, SLE = systemic lupus erythematosus

CASE 2

A patient with a medical history of hyperthyroidism, hepatitis C, and ocular cicatricial pemphigoid who had been treated with steroids and cyclophosphamide presented with a flare of ocular cicatricial pemphigoid following a remission of 7 years. The flare was treated with high dose steroids (60 mg of prednisone), and remission was achieved. Three more flares occurred during the following year and the patient was treated with increasing doses of prednisone. One year after remission, the patient complained of loss of appetite, weight loss, and back pain. A full-body CT scan revealed a pancreatic tumor and bone metastases. The patient died within a year. This case describes paraneoplastic syndrome masquerading as an exacerbation of an autoimmune disease following a long-standing remission.

CASE 3

A patient with a past medical history of chronic obstructive lung disease and breast cancer presented with a de novo painful and cyanotic digit of the right hand for several days without trauma to the digit or similar past events. The patient denied decreased appetite, night sweats, weight loss, systemic fever, or Raynaud's phenomenon. The only new medications listed were aspirin and tamoxifen. The physical evaluation was normal except tenderness and cyanosis of the third digit of the right hand. Blood laboratory tests showed normal range complete blood count as well as normal renal, liver, and thyroid function. Hypercoagulability tests were negative. Autoimmune serologies including antinuclear antibody (ANA), anticardiolipin, and anti-β2-glycoproteins were also negative. Imaging investigation included arterial and venous ultrasound Doppler of the right hand, cardiac echography, and full-body CT scan, which were all normal. Despite appropriate medical therapy for digital ischemic necrosis, with aspirin and enoxaparin, the patient's symptoms escalated with severe pain and extension of cyanosis to all digits on the right hand, affecting the third and fourth digits of the left hand as well. Opioid therapy and intravenous Iloprost therapy for 3 weeks was initiated without significant clinical results. Eventually the patient developed auto-amputation of the third and fourth digits of the right hand and calcinosis of the digital beds. Following this dramatic clinical presentation, repeated serologic tests were performed. High titers of ANA 1:320 and anti-centromere antibodies were found. The patient was then diagnosed with systemic sclerosis since scleroderma manifested by digital ulcers and appropriate serology without skin involvement. The patient began therapy with bosentan 125 mg twice a day with a rapid clinical improvement. During a period of 8 weeks, the necrotic areas disappeared, and no new digital ulcers reappeared. Due to the atypical presentation of her scleroderma, a full-body CT scan was performed, and no malignancy was found. Nevertheless, a further full-body CT scan was performed 6 and 12 months later. A 1 cm nodule in the left lower lobe of the lung was discovered after one year of follow-up. The pathology report from the lung nodule biopsy revealed adenocarcinoma of the lung. Following oncologic therapy, the digital ulceration remitted, and the patient remained asymptomatic for two years. This case emphasizes the need for repeat CT scans in atypical patients.

CASE 4

A patient with a history of silicone breast implants presented with mild cognitive impairment, palpitations, and bilateral lower leg neuropathy over a 3-year period. A lower leg skin biopsy revealed small fiber neuropathy. Autoimmune serologic investigations were negative. A clinical suspicion of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) syndrome was proposed due to the combination of cognitive, cardiac, and peripheral nerve manifestations in the context of silicone breast implants that were later removed. The patient was treated with IVIG therapy with a good

clinical response. On a periodic follow-up of laboratory blood tests, calcium levels were slightly elevated, parathyroid hormone level was normal, and titers of anti-thyroid peroxidase remained positive for 3 years. The patient underwent a thyroid gland sonography that showed a suspicious right lobe nodule. A nodule biopsy confirmed papillary thyroid carcinoma. This case emphasizes that in the differential diagnosis of ASIA syndrome, paraneoplastic syndrome should also be considered. Table 1 summarizes our findings.

COMMENT

Autoimmune paraneoplastic syndromes should be considered by a physician when patients present with a personal medical history of a prior malignancy or a family history of cancer. In addition, age of onset above 50 years, systemic clinical manifestations such as loss of appetite, loss of weight, night sweats, fever, and a reasonable timeline between the autoimmune paraneoplastic manifestation and the diagnosis of cancer may suggest this association. The differential diagnosis of paraneoplastic polyarthritis includes RA, SLE, systemic sclerosis, and polymyalgia rheumatica.

Specific abnormal findings include inappropriate pain levels, other findings on the physical examination (clubbing, lymphadenopathy), and lack of response to disease-modifying antirheumatic drugs or steroids. The screening for the type of malignancy is the same as for the non-autoimmune population [5]. In addition, a rapid onset of inflammatory arthritis, autoimmune disease with poor response to standard of care, and a clinical improvement after cancer therapy should raise the possibility of an autoimmune paraneoplastic syndrome. Recurrence of autoimmune paraneoplastic symptoms could indicate recurrence of malignancy [4].

We described other unique manifestations of autoimmune paraneoplastic syndrome. First, a flare-up of autoimmune disease following a prolonged period of remission may be the beckoning of early cancer (cases 1 and 2). In addition, while the malignancy may not initially be intense, clinicians should continue to search for the occult cancer by repeated CT (case 3). Last, ASIA syndrome may indicate a malignancy (case 4).

CONCLUSIONS

Autoimmune paraneoplastic syndromes have not been extensively studied. Autoimmune disease exacerbation after long-standing remission should raise suspicion and lead to further investigation for malignancy. In atypical autoimmune disease manifestations, repeat CT scans over a year may lead to an early diagnosis of cancer. Constitutional findings are common in autoimmune disease, but when occurring in the elderly population, a search for malignancy is good clinical practice. To the best of our knowledge, we are the first to present a case report of ASIA syndrome heralding occult malignancy.

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Many who have spent a lifetime in it can tell us less of love than the child that lost a dog yesterday.
Thornton Wilder (1897–1975), American playwright and novelist

We are a landscape of all we have seen.
Isamu Noguchi (1904–1988), sculptor and architect

We read books to find out who we are.
Ursula K. Le Guin (1929–2018), American author best known for her works of speculative fiction, including science fiction works set in her Hainish universe, and the Earthsea fantasy series