Paraneoplastic Musculoskeletal Syndromes

Fahad Khan, MD[1], Hilary Kleppel, BS[1], Alexa Meara, MD*

KEYWORDS

• Paraneoplastic • Rheumatologic • Cancer • Malignancy • Dermatomyositis

KEY POINTS

- Clinical changes that may represent paraneoplastic phenomena should cue physicians to be vigilant for a concomitant or impending underlying malignancy.
- Treatment of a culprit malignancy can result in the resolution or amelioration of the associated paraneoplastic phenomenon.
- Atypical presentations of clinical entities not often thought to be related to cancer, such as Raynaud phenomenon or polymyalgia rheumatica, may serve as clues to their manifestation as paraneoplastic phenomena.
- When a paraneoplastic phenomenon is encountered, physicians should strongly consider a focused work-up for associated cancers, especially with new diagnoses of dermatomyositis.

INTRODUCTION

Paraneoplastic syndromes are diseases caused by malignancies through means other than mass effect or metastasis.[1] Even though they occur in only about 10% of patients with cancer, physicians are wise to be vigilant for them for several reasons: a paraneoplastic phenomenon can be the first sign of cancer in an undiagnosed individual, and it can be severe enough to cause death.[2] Despite the tumor being distinctly separate from the area where the paraneoplastic syndrome manifests, it is important to realize that paraneoplastic phenomena are not caused by metastases of the neoplasm. For example, hypercalcemia caused by osteolysis caused by bony metastases does not count as a paraneoplastic disease, but hypercalcemia from production of parathyroid hormone–related protein by a tumor does. Paraneoplastic rheumatic syndromes can occur with hematologic cancers, lymphoproliferative diseases, and solid tumors.[3] Diseases that feature an advanced age at onset, significant constitutional upset, inadequate response to treatment, and otherwise atypical characteristics should increase the index of suspicion for a paraneoplastic syndrome.

Division of Rheumatology and Immunology, Department of Internal Medicine, Columbus, OH, USA
[1] Present address: 543 Taylor Avenue, Columbus, OH 43203.
* Corresponding author. 543 Taylor Avenue, Columbus, OH 43203.
E-mail address: alexa.meara@osumc.edu

Rheum Dis Clin N Am 46 (2020) 577–586
https://doi.org/10.1016/j.rdc.2020.04.002 **rheumatic.theclinics.com**

SPECIFIC PARANEOPLASTIC SYNDROMES

Arthropathy

Carcinomatous polyarthritis (CP) is arthritis in the setting of malignancy that is not caused by the mass effect of a tumor or space-occupying effect of its metastases.[3] Solid tumors of the oropharynx, larynx, esophagus, stomach, colon, lung, breast, ovary, and pancreas, as well as lymphoproliferative diseases, have been associated with CP.[4] CP generally affects patients older than 50 years and is rapidly progressive on onset, which is often around the time of diagnosis of the responsible cancer. It is a diagnosis of exclusion that must be distinguished from other diseases, such as seronegative spondyloarthropathies (eg, reactive arthritis and enteric arthritis) and crystalline arthropathies. Distinguishing between CP and rheumatoid arthritis (RA) can pose a challenge, because both entities feature an increasing incidence with age and similar clinical presentations. In general, CP differs from RA in its asymmetric distribution, predilection for joints in the legs rather than wrists and hands, and seronegativity for the rheumatoid factor (RF) and anti–cyclic citrullinated peptide (CCP) antibodies.[5] However, there are reports of CP presenting with symmetric involvement of the wrists and hands as well as RF and anti-CCP antibody positivity.[5,6] The RF positivity may be explained by the malignancy. Although these features may render it difficult to exclude the possibility of RA, CP should eventually reveal a temporal association with a malignancy, whose treatment should resolve the arthritis symptoms.[7] For example, a 44-year-old woman who developed an aggressive polyarthritis was found to have medullary carcinoma of the breast and experienced resolution of her arthritis a week after mastectomy[8] without recurrence over a year of surveillance. Similarly, a 43-year-old man with CP associated with bronchogenic carcinoma experienced complete resolution of his arthritis following treatment with cisplatinum and etoposide.[6] In that case, it is not possible to say whether treatment of the underlying malignancy effected an enduring cure of the associated CP, because his health soon declined, and the patient died. However, the investigators conclude their report by stating that the treatment of CP is tantamount to treatment of the associated cancer, and that recurrence of arthritis should increase suspicion for recurrence of cancer.

Hypertrophic osteoarthropathy (HOA) causes proliferation of skin and bone associated with effusions in large joints.[9] Patients experience a progressive and bilateral periostosis at tubular bones, such as the tibia and fibula. Although HOA can be a primary disorder, it can also be secondary to numerous causes, among which are malignancies of the pulmonary and gastrointestinal systems. Symptomatic patients report leg pain and tenderness. The predominant physical examination finding in HOA is digital clubbing, which is a bulbous change of the distal part of the fingers associated with a convex deformity of the nails. In addition, there may be hypertrophy of the skin in the nailbeds or face. If a large joint effusion is aspirated, synovial fluid analysis reveals an increased viscosity and a paucity of white blood cells. A 1988 literature review of primary HOA found that synovial fluid analysis of joint effusions in 9 instances revealed thick, viscous fluid with low counts of white blood cells.[10] The synovial fluid was noninflammatory except for 1 case, which showed hemarthrosis. Plain films show periostosis as a thickened cortex of affected bones. HOA can be associated with lung malignancies,[11] especially non–small cell lung cancer.[12] Secondary causes of HOA are usually pulmonary but can also be pleural, mediastinal, or cardiovascular malignancies. Gastrointestinal tumors have also been linked to HOA. When it is associated with cancer, HOA can regress with treatment of the underlying malignancy.[13] Patients who have HOA in the setting of cystic fibrosis (CF) have been managed with nonsteroidal antiinflammatory drugs, physical therapy, and steroids. A 2002 case report

describes a patient with CF who was treated with serial doses of pamidronate and experienced full resolution of symptoms with each.[14] Furthermore, a 2009 review of the use of pamidronate in various rheumatic conditions reports that it has been very effective for analgesia in primary as well as paraneoplastic HOA.[15]

Remitting seronegative symmetric synovitis with pitting edema (RS3PE) can exist as a primary disorder or occur secondary to malignancy.[13] In addition, patients with RS3PE have a higher incidence of malignancy.[16] RS3PE can occur with cancers of the stomach, colon, prostate, ovary, and endometrium, as well as malignant lymphoma, leukemia, and myelodyspasias.[13,16] When secondary to a malignancy, patients may have fever, weight loss, and an inadequate response to steroids. RS3PE has a predilection for the elderly and features bilateral synovitis and edema of the hands and feet.[17] Edema can lend a boxing-glove appearance to the hands.[13] Laboratory investigations reveal increase of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and absence of RF and anti-CCP antibodies.[17]

Polymyalgia rheumatica (PMR) is a disease of the elderly that causes pain and stiffness in the proximal muscles as well as fatigue.[3] Laboratory investigation typically shows anemia of chronic disease and increased ESR. One of the hallmarks of PMR is a dramatic response to a moderate dose of steroids; for example, 20 mg of prednisone daily. The following atypical features may be clues to an underlying cancer: onset before 50 years of age, asymmetric distribution, profound anemia, proteinuria, ESR greater than 100 mm/h or less than 40 mm/h, and an inadequate response to steroids.[3] Atypical PMR (aPMR) can precede a cancer diagnosis by up to about a year and has been associated with malignancies of the kidney, lung, and colon, and multiple myeloma.[3,13] Treatment of the underlying malignancy may alleviate symptoms of aPMR. A 2016 case report from Portugal describes an 82-year-old man with disabling pain and stiffness of his shoulders and hips associated with increased ESR and CRP level who was diagnosed with PMR and started on a steroid called deflazacort, 12 mg daily, but experienced inadequate relief despite increasing the dose to 18 mg daily. Further investigation of incidental macroscopic hematuria revealed diagnoses of bladder and prostate cancer, which were treated with radical cystectomy and prostatectomy; the patient was asymptomatic 1 month following discharge and showed improvement in inflammatory markers.[18,19]

Gout is a well-known inflammatory arthritis that can exist by itself, but it can also be secondary to the hyperuricemia that results from accelerated nucleic acid breakdown in patients with malignancy undergoing chemotherapy and radiation.[13] Hematologic malignancies such as leukemia, polycythemia vera, and lymphoma are associated with gout.[7] Liver involvement by the malignancy can affect the severity of gout. In addition, chemotherapy used to treat malignancy can lead to gout, because radiation or antiblastic therapies can cause hyperuricemia.[13]

Amyloidosis is the deposition of insoluble amyloid protein that can cause organ failure. Amyloidosis can also affect the synovium and periarticular space leading to joint pain, most commonly in the shoulders, wrists, and knees.[13] A low-grade but frank arthritis may be seen in an asymmetric pattern in multiple myeloma and Waldenström macroglobulinemia.

Myopathy

Inflammatory myopathy is an immune-mediated attack on skeletal muscle that manifests in weakness.[3] Dermatomyositis (DM) seems to have the strongest association with malignancy out of all the types of autoimmune myopathies, because 6% to 60% of patients with DM develop malignancy. The malignancy is usually diagnosed within a couple of years into the diagnosis of DM, and associated cancers include

ovarian, lung, gastric, and nasopharyngeal types. Patients with polymyositis are also at increased risk for developing cancer, with up to 28% developing malignancy. Clinically amyopathic DM is also associated with cancer. Patients with inflammatory myopathy in whom to be especially vigilant about underlying malignancy include those with the following features: diagnosis at age greater than 50 years, male sex, rapidly progressive course, shawl sign, distal weakness, weakness of the pharynx and diaphragm, difficult-to-treat disease, leukocytoclastic vasculitis (LCV), skin ulceration/necrosis/vasculitis, lack of lung involvement, increased creatine kinase level, increased ESR, increased CRP level, anti–p155-140 (anti–transcriptional intermediary factor-1γ) antibody, and anti–nuclear matrix protein (NXP)-2 (anti-MJ) antibody. Treatment of the underlying malignancy can lead to improvement of the associated myopathy and cutaneous manifestations.[20] Cancer-associated myositis (CAM) and the malignancy of which it is a paraneoplastic phenomenon can have a parallel clinical course, and a relapse of malignancy can be accompanied by a similar resurgence of myositis. Patients with CAM rarely have myositis-specific and myositis-associated autoantibodies. The features of an inflammatory myopathy that are associated with a lower risk of cancer include the anti–Jo-1 antibody, anti-extractable nuclear antigens(includes Anti-SM, Anti-RNP, anti-RO/LA) antibodies, interstitial lung disease, joint involvement, and Raynaud phenomenon.[3] Age-appropriate cancer screening should be ensured in patients with inflammatory myopathy, and this vigilance for underlying cancer should be continued in case the malignancy develops years after the myopathy. Other means of discovering a malignancy in this setting include imaging the chest, abdomen, and pelvis and checking serum levels of tumor markers.

Vascular

Cancer-associated vasculitis affects about 8% of patients with malignancy,[3] complicates lymphoproliferative and myeloproliferative diseases more than solid tumors, and may antedate the discovery of cancer. It is generally a small vessel vasculitis that affects the skin rather than internal organs. Although cutaneous vasculitis and polyarteritis nodosa (PAN) are the most frequent paraneoplastic vasculitides,[21] the central nervous and cardiovascular systems can also be affected. Cutaneous vasculitis most commonly presents with palpable purpura of the legs but can also cause urticaria and erythema elevatum diutinum.

LCV is a small vessel vasculitis that presents with palpable purpura with a predilection for the legs, arthralgias, arthritis, myalgias, and fever.[13] LCV has connections with lymphoproliferative disorders such as acute and chronic leukemias, lymphomas, myelodysplasias, and solid tumors.

PAN is a systemic necrotizing vasculitis with a predilection for medium-sized vessels.[13] Patients are generally seronegative for antineutrophil cytoplasmic autoantibodies (ANCA) and do not experience glomerulonephritis or pulmonary capillaritis, which serves to distinguish PAN from microscopic polyangiitis, which is an ANCA-associated vasculitis (AAV) that can also target small and medium-sized vessels.[22] Inflamed arteries may occlude or rupture, causing ischemia or hemorrhage in various organs. Patients can experience fever; malaise; weight loss; pain in the abdomen, joints, and muscles; paresthesia; orchitis; and high blood pressure.[21] The most commonly affected areas are the peripheral nervous system and skin. The most frequent neurologic derangement is mononeuritis multiplex, whereas the skin examination may show palpable purpura, livedoid changes, nodules, and ulcers. Kidneys can be affected by infarctions or hematomas secondary to ruptured microaneurysms, and those infarcts can go on to cause hematuria and proteinuria. Hypertension can occur from vasculitis of intrarenal vasculature. About 10% of cases are mostly limited

to skin involvement, and those have a better course. Systemic PAN may be associated with hepatitis B infection or hairy-cell leukemia.[23,24] PAN is associated with solid tumors of the liver, colon, bladder, lung, and hypopharynx, and hematologic diseases such as leukemia and myelodysplasia.[13] Granulomatosis with polyangiitis, an AAV, may be temporally linked to renal cell carcinoma.[25] Cryoglobulinemia is the presence of immunoglobulins in the serum that precipitates at less than 37°C.[13] Of the 3 types of cryoglobulinemia recognized, type I has an association with malignancy. Type I cryoglobulinemia consists of monoclonal immunoglobulin (Ig) M IgG and is associated with Waldenström macroglobulinemia and multiple myeloma. It can cause symptoms of hyperviscosity, such as vertigo, encephalopathy, cephalgia, and stroke.[26] Types II and III feature both IgM and IgG and are therefore called mixed cryoglobulinemia. Most cases of type II cryoglobulinemia are associated with hepatitis C infection, whereas type III cryoglobulinemia can result from infections and autoimmune disorders. Approximately 15% of patients with type II or type III cryoglobulinemia develop vasculitis, and almost all of those experience skin disease, such as palpable purpura.[21] About 6% of patients with cryoglobulinemic vasculitis have a lymphoproliferative disorder. Patients with mixed cryoglobulinemia have a high risk for developing non-Hodgkin lymphoma.[13] Treatment of paraneoplastic vasculitis begins with identifying and treating the underlying neoplasm, because that may help resolve the cutaneous rash. In addition, most patients should receive systemic steroids and, if need be, steroid-sparing agents such as cyclophosphamide, methotrexate, or azathioprine.

Erythromelalgia causes erythema and a sensation of burning and heat in the arms and legs, with a preference for the feet. The face and ears can also be involved, and there may be swelling in addition to redness and warmth.[21] The onset ranges from sudden to gradual, and aggravating factors include exercise, heat, and dependency of the affected limb.[3] Relieving factors include cold temperature and limb elevation. Although erythromelalgia may exist as a primary disorder, it can also be associated with myeloproliferative diseases such as polycythemia vera and essential thrombocytosis. The pathophysiology is thought to be thrombocythemia or arteriovenous shunting. Breakdown products and microthrombi of platelets are also implicated. Treatment with aspirin can palliate the symptoms of erythromelalgia. Despite palliation of symptoms with aspirin, patients should be monitored periodically with complete blood counts, because paraneoplastic erythromelalgia can precede the diagnosis of an associated cancer.[25]

Severe, asymmetric Raynaud phenomenon (RP) that occurs after age 50 years and leads to digital necrosis can be a paraneoplastic phenomenon that warrants a pursuit of an underlying malignancy.[3] In a 2014 retrospective cohort study from France, 15% of patients admitted for an initial occurrence of digital ischemia had an underlying cancer; those associated malignancies included adenocarcinoma, squamous cell carcinoma, and lymphoid neoplasia.[27] Other cancer associations include gastrointestinal, lung, ovarian, and renal carcinomas[7] and sarcomas.[13] RP can precede the cancer diagnosis by 7 to 9 months. The development of digital necrosis in the setting of DM should especially cue physicians to consider the possibility of an underlying cancer.

Cutaneous

Systemic sclerosis (SSc) can occur around the time of diagnosis of a malignancy. Also, cutaneous lesions similar to those seen in SSc can occur in several cancers and are called pseudoscleroderma or pseudosclerosis.[13] Associated cancers include metastatic melanoma; osteoclastic myeloma; plasmacytomas; carcinoids; and gastric, breast, and lung tumors.[7] In addition, the plasma cell dyscrasia POEMS

(polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome can result in sclerodermoid skin changes. Although technically not a paraneoplastic phenomenon, sclerodermoid skin changes can also be seen in patients with hematologic malignancy who develop chronic graft-versus-host disease following bone marrow transplant.[25]

Fasciitis-panniculitis syndrome (FPS) causes swelling and hardening of the skin and subcutis and is accompanied by fibrosis and inflammation.[3] Patients may experience a monoarticular or polyarticular arthritis and subcutaneous nodules. FPS can exist as a primary disorder or be secondary to various causes such as infection or trauma. Rarely, FPS can be associated with cancer. Associated cancers include myelomonocytic leukemia, chronic lymphocytic leukemia, myeloproliferative disorder, Hodgkin disease, T-cell lymphoma, breast carcinoma, prostate carcinoma, gastric adenocarcinoma, and pancreatic carcinoma.[28] When FPS occurs as a paraneoplastic phenomenon, it has a female predilection and poor response to prednisone. Eosinophilic fasciitis (EF) is in the category of FPS and mostly affects the limbs, causing pain and swelling because of induration of the skin.[3,13] Laboratory investigations reveal hypereosinophilia, hypergammaglobulinemia, and increased ESR. Malignancies associated with EF include Hodgkin disease, lymphoproliferative disorder, angioimmunoblastic lymphadenopathy, and peripheral T-cell lymphoma.[29]

Multicentric reticulohistiocytosis (MRH) presents with papules located on the face, dorsal hands, and periungual areas.[3] It is associated with a symmetric and erosive polyarthritis that affects the interphalangeal joints, wrists, elbows, shoulders, hips, knees, ankles, and feet.[30] Patients can develop arthritis mutilans. In addition to skin and joint involvement, MRH can affect internal organs such as the thyroid, heart, lungs, liver, and lymph nodes.[13] Biopsy of affected areas characteristically shows infiltration by histiocytes and multinucleated giant cells. MRH can be associated with lung, stomach, breast, cervix, colon, and ovarian cancer. Treatment agents include prednisone, methotrexate, and etanercept.

Palmar fasciitis (PF) is a fibrosing condition of the palmar fascia associated with bilateral finger contractures and inflammatory polyarthritis.[3] The most common sites of arthritis are the metacarpophalangeal and proximal interphalangeal joints, but the wrists, elbows, knees, ankles, and feet can also be involved. PF is almost always associated with an underlying cancer, such as that of the ovaries, breast, uterus, lung, stomach, pancreas,[13] or endometrium.[7] Leukemia and Hodgkin disease may also play a role.

Miscellaneous

Antiphospholipid antibody (aPL) positivity has a known association with thrombotic disease in primary antiphospholipid syndrome as well as a condition secondary to autoimmune diseases such as systemic lupus erythematosus.[3] Recent work has also revealed an association of aPLs with cancer, but an association of aPLs in this patient population with thromboembolism is less clear. Although the prevalence of aPLs in the general population is 1% to 5%, it is higher in patients who have solid malignancies or lymphoproliferative diseases. For example, a 1995 study comparing 216 patients with cancer with 88 healthy controls found an approximately 22% prevalence of anticardiolipin antibodies in the cancer arm and only approximately 3% in the control arm.[31] Rates of thromboembolism were much higher in patients with cancer with anticardiolipin antibodies (28%) compared with rates of thromboembolism in patients with cancer without anticardiolipin antibodies (14%). In a more recent prospective cohort study from 2014, 74% of 95 patients with cancer admitted to an intensive care unit had aPL antibodies.[32] However, vascular complication rates in that cohort

were similar in patients with and without aPL antibodies. aPL positivity is associated with multiple types of cancer, including carcinoma of the stomach, colon, prostate, ovary, lung, kidney, liver, and breast, and B-cell lymphoma, chronic myeloid lymphoma, non-Hodgkin lymphoma, lymphoblastic leukemia, monocytic leukemia, and myelomonocytic leukemia.[33,34]Thrombotic events in aPL-positive patients may herald an underlying malignancy.[34] In a patient with venous thromboembolism and ovarian endometrial adenocarcinoma, surgical excision of the tumor was followed by disappearance of lupus anticoagulant and anticardiolipin antibody, suggesting that the cancer possibly induced the aPL antibodies[35] and hematologic malignancies alike.

Reflex sympathetic dystrophy (RSD), also called complex regional pain syndrome (CRPS), entails local pain, edema, vasomotor changes, and osteoporosis confined to a particular extremity.[3] The pathogenesis is thought to be sympathetic dysfunction, and it can be caused by stroke, heart attack, injury, or various malignancies, such as apical lung tumors. Such Pancoast tumors may disrupt the brachial plexus or the stellate ganglion and cause RSD. CRPS has also been associated with occult neoplasms of the brain, breast, bowel, and ovaries.[36] In rare cases, CRPS can be associated with the peripheral musculoskeletal tumors osteoid osteoma and epithelioid sarcoma. RSD may improve as the associated cancer is treated.

Oncogenic osteomalacia, also known as tumor-induced osteomalacia, results in renal phosphate wasting and causes severe biochemical and skeletal changes.[37] It is a rare paraneoplastic phenomenon associated with cancers that evolve fibroblast growth factor-23.[3] Osteomalacia refers to soft bones from inadequate calcification caused by kidney disease or vitamin D deficiency. Patients develop chronic, progressive pain in muscles and bones, fatigue, weakness, and recurrent fractures. In children, it may mimic rickets with signs such as gait abnormality, stunted growth, and skeletal changes. Laboratory investigations reveal hypophosphatemia, phosphaturia, and low or normal serum calcitriol level. (Normally, calcitriol level should be increased in the setting of hypophosphatemia.) The serum phosphorus level can be severely low (eg, 0.7 mg/dL). Bone histomorphometry reveals osteomalacia. Plain films may show diffuse osteopenia, pseudofractures, and coarsening of trabeculae. The fractures result from inadequate calcitriol production and renal phosphate wasting. The culprit tumors may be small, indolent, and unusually located; for example, in the craniofacial regions and extremities. Oncogenic osteomalacia may result from malignant or benign tumors, such as those originating from mesenchymal cells.[7] Removing the responsible tumor can lead to quick normalization of the biochemical abnormalities and remineralization of bone. If resection is not possible because of inability to identify the occult malignancy responsible, then medical management with phosphorus and calcitriol is indicated.

Sarcoidosis is not the only condition that causes noncaseating granulomas, because similar-appearing granulomas can be identified in lymph nodes that drain areas with cancer involvement.[3] Solid tumors and lymphomas are both associated with granuloma formation. Therefore, patients with presumed sarcoidosis should be thoroughly evaluated for an underlying malignancy. An increased risk of lung cancer, bile duct cancer, colorectal cancers, and lymphoma has been reported in the presence of sarcoidosis.[38]

Lymphomatoid granulomatosis (LG) is a lymphoproliferative disease that features lymphocytic infiltration of blood vessels.[3] It is angiodestructive; can affect the lungs, skin, and central nervous system; and carries a poor prognosis. LG has historically been associated with T-cell lymphomas.[39] A quarter of affected patients go on to develop lymphoma. In addition to lymphoma, LG may be associated with leukemia. It mostly affects middle-aged patients and has a male predilection.[40] Patients present

with fever and cough. Plain films may show numerous, bilateral, nodular pulmonary infiltrates. The skin and nervous system are the most frequently affected sites outside the lungs. Pathology shows vascular infiltration by mononuclear cells and necrosis, cluster of differentiation (CD)-20 positive B cells, CD-3–positive T cells, plasma cells, and histiocytes. LG carries a mortality as high as 71%, with most deaths occurring within 2 years.

SUMMARY

Although cancers can cause morbidity and mortality through mass effect of the primary tumor or its metastases, they are also capable of exerting distant effects through paraneoplastic phenomena. Many types of paraneoplastic phenomena exist, including those relevant to rheumatology and the musculoskeletal system that affect the joints, muscles, vasculature, skin, and bones.

Clinics Care Points

- Clinical changes that may represent paraneoplastic phenomena should cue the physician to be vigilant for a concomitant or impending underlying malignancy.
- Treatment of a culprit malignancy can result in the resolution or amelioration of the associated paraneoplastic phenomenon.
- Atypical presentations of clinical entities not often thought to be related to cancer, such as RP or PMR, may serve as clues to their manifestation as paraneoplastic phenomena.
- When a paraneoplastic phenomenon is encountered, physicians should strongly consider a focused work-up for associated cancers, especially with new diagnoses of DM.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Jameson JL, Longo DL. Paraneoplastic syndromes: endocrinologic/hematologic. In: Jameson JL, Fauci AS, Kasper DL, et al, editors. Harrison's principles of internal medicine. 20th edition. New York: McGraw-Hill Education; 2018.
2. Schoen FJ, Mitchell RN. Neoplasia. In: Robbins & Cotran pathologic basis of disease. 9th edition. Philadelphia, PA: Saunders/Elsevier; 2015. p. 265–340.
3. Vaseer S, Chakravarty EF. Musculoskeletal syndromes in malignancy. In: Kelley and Firestein's textbook of rheumatology. 10th edition. Philadelphia, PA: Saunders/Elsevier; 2017. p. 2048–65, e2046.
4. Gamage KKK, Rifath MIM, Fernando H. Migratory polyarthritis as a paraneoplastic syndrome in a patient with diffuse large B cell lymphoma: a case report. J Med Case Rep 2018;12(1):189.
5. Watson GA, O'Neill L, Law R, et al. Migrating polyarthritis as a feature of occult malignancy: 2 case reports and a review of the literature. Case Rep Oncol Med 2015;2015:934039.
6. Zupancic M, Annamalai A, Brenneman J, et al. Migratory polyarthritis as a paraneoplastic syndrome. J Gen Intern Med 2008;23(12):2136–9.
7. Sendur OF. Paraneoplastic rheumatic disorders. Archives of Rheumatology 2012; 27(1):18–23.

8. Chan MK, Hendrickson CS, Taylor KE. Polyarthritis associated with breast carcinoma. West J Med 1982;137(2):132–3.
9. Mader R. Proliferative bone diseases. In: Kelley and Firestein's textbook of rheumatology. 10th edition. Philadelphia, PA: Saunders/Elsevier; 2017. p. 1751–63.e3.
10. Martínez-Lavín M, Pineda C, Valdez T, et al. Primary hypertrophic osteoarthropathy. Semin Arthritis Rheum 1988;17(3):156–62.
11. Bozzao F, Bernardi S, Dore F, et al. Hypertrophic osteoarthropathy mimicking a reactive arthritis: a case report and review of the literature. BMC Musculoskelet Disord 2018;19(1):1–6.
12. Yap FY, Skalski MR, Patel DB, et al. Hypertrophic osteoarthropathy: clinical and imaging features. Radiographics 2017;37(1):157–95.
13. Manzini CU, Colaci M, Ferri C, et al. Paraneoplastic rheumatic disorders: a narrative review. 2018. Available at: https://wwwreumatismoorg/indexphp/reuma.
14. Garske LA, Bell SC. Pamidronate results in symptom control of hypertrophic pulmonary osteoarthropathy in cystic fibrosis. Chest 2002;121(4):1363–4.
15. Slobodin G, Rosner I, Feld J, et al. Pamidronate treatment in rheumatology practice: a comprehensive review. Clin Rheumatol 2009;28(12):1359–64.
16. Sakamoto T, Ota S, Haruyama T, et al. A case of paraneoplastic remitting seronegative symmetrical synovitis with pitting edema syndrome improved by chemotherapy. Case Rep Oncol 2017;10:1131–7.
17. Parperis K, Constantinidou A, Panos G. Paraneoplastic arthritides: insights to pathogenesis, diagnostic approach, and treatment. J Clin Rheumatol 2019. https://doi.org/10.1097/RHU.0000000000001202.
18. Pereira J, Eugénio G, Calretas S, et al. More than just a case of polymyalgia rheumatica. Eur J Case Rep Intern Med 2016;3. Available at: https://www-ncbi-nlm-nih-gov.proxy.lib.ohio-state.edu/pmc/articles/PMC6346904/pdf/374-1-2612-1-10-20160223.pdf.
19. West SG. Idiopathic inflammatory myopathies. In: Rheumatology secrets. 4th edition. Philadelphia, PA: Elsevier Health Sciences; 2020. p. 177–84.
20. Ponyi A, Constantin T, Garami M, et al. Cancer-associated myositis: clinical features and prognostic signs. Ann N Y Acad Sci 2005;1051(1):64–71.
21. Buggiani G, Krysenka A, Grazzini M, et al. Paraneoplastic vasculitis and paraneoplastic vascular syndromes. Dermatol Ther 2010;23(6):597–605.
22. Hernandez-Rodriguez J, Alba MA, Prieto-Gonzalez S, et al. Diagnosis and classification of polyarteritis nodosa. J Autoimmun 2014;48-49:84–9.
23. Elkon KB, Hughes GRV, Catovsky D, et al. Hairy-cell leukæmia with polyarthritis nodosa. Lancet 1979;314(8137):280–2.
24. Vankalakunti M, Joshi K, Jain S, et al. Polyarteritis nodosa in hairy cell leukaemia: an autopsy report. J Clin Pathol 2007;60(10):1181–2.
25. Fam AG. Paraneoplastic rheumatic syndromes. Baillieres Best Pract Res Clin Rheumatol 2000;14(3):515–33.
26. Stone JH. Immune complex–mediated small-vessel vasculitis. In: Kelley and Firestein's textbook of rheumatology. 10th edition. Philadelphia, PA: Saunders/Elsevier; 2017. p. 1571–80.
27. Le Besnerais M, Miranda S, Cailleux N, et al. Digital ischemia associated with cancer: results from a cohort study. Medicine (Baltimore) 2014;93(10):e47.
28. Shah A, Jack A, Liu H, et al. Neoplastic/paraneoplastic dermatitis, fasciitis, and panniculitis. Rheum Dis Clin North Am 2011;37(4):573–92.
29. Khanna D, Verity A, Grossman J. Eosinophilic fasciitis with multiple myeloma: a new haematological association. Ann Rheum Dis 2002;61(12):1111–2.

30. Chauhan A, Mikulik Z, Hackshaw KV. Multicentric reticulohistiocytosis with positive anticyclic citrullinated antibodies. J Natl Med Assoc 2007;99(6):678–80.
31. Zuckerman E, Toubi E, Golan TD, et al. Increased thromboembolic incidence in anti-cardiolipin-positive patients with malignancy. Br J Cancer 1995;72(2):447–51.
32. Vassalo J, Spector N, de Meis E, et al. Antiphospholipid antibodies in critically ill patients with cancer: a prospective cohort study. J Crit Care 2014;29(4):533–8.
33. Gomez-Puerta JA, Cervera R, Espinosa G, et al. Antiphospholipid antibodies associated with malignancies: clinical and pathological characteristics of 120 patients. Semin Arthritis Rheum 2006;35(5):322–32.
34. Miesbach W. Antiphospholipid antibodies and antiphospholipid syndrome in patients with malignancies: features, incidence, identification, and treatment. Semin Thromb Hemost 2008;34(3):282–5.
35. Asherson RA. Antiphospholipid antibodies, malignancies and paraproteinemias. J Autoimmun 2000;15(2):117–22.
36. Lipton S, Schwab P. Neoplasm mimics of rheumatologic presentations: sialadenitis, ocular masquerade syndromes, retroperitoneal fibrosis, and regional pain syndromes. Rheum Dis Clin North Am 2011;37(4):623–37.
37. Jan de Beur SM. Tumor-induced osteomalacia. JAMA 2005;294(10):1260–7.
38. Herron M, Chong SG, Gleeson L, et al. Paraneoplastic sarcoidosis: a review. QJM 2020;113(1):17–9.
39. Alexandra G, Claudia G. Lymphomatoid granulomatosis mimicking cancer and sarcoidosis. Ann Hematol 2019;98:1309–11.
40. Katzenstein A-LA, Doxtader E, Narendra S. Lymphomatoid granulomatosis: insights gained over 4 decades. Am J Surg Pathol 2010;34(12):e35–48.