Migratory Polyarthritis as a Paraneoplastic Syndrome

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Carcinomatous polyarthritis (CP) is a rare paraneoplastic disorder that has been associated with a variety of solid tumors. It presents in a similar manner to other polyarticular disorders and often precedes detection of the underlying malignancy, making recognition critical. CP responds to the treatment of the neoplastic process. We present a patient who initially presented with asymmetric inflammatory polyarthritis who was later diagnosed with bronchogenic carcinoma. Following the case report we present our learning objectives, which include the differential diagnosis of inflammatory polyarthritis, diagnostic approach to CP, and features that distinguish it from other more common causes of polyarthritis. We conclude with a brief discussion of the pathophysiology and management of CP.

KEY WORDS: carcinomatous polyarthritis; migratory arthritis; paraneoplastic syndrome.
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BACKGROUND

Malignant disease is associated with a wide variety of paraneoplastic syndromes involving multiple organ systems, including the musculoskeletal system. The musculoskeletal system can be affected by direct invasion of the primary tumor, metastasis, synovial reaction to juxta-articular masses, and, indirectly, by the effects of a distant tumor. The latter, referred to as a paraneoplastic syndrome, is thought to be the result of humoral mechanisms. Paraneoplastic disorders are defined by the following criteria: they must occur during the course of an identified malignant disease or precede clinical evidence of a malignancy, symptoms cannot be the result of direct tumor invasion or compression, and symptoms improve with treatment of the underlining neoplasm[1]. Diagnosis of a paraneoplastic syndrome can be challenging in the absence of a known malignancy. Carcinomatous polyarthritis (CP) is a paraneoplastic syndrome that has been described in bronchogenic carcinoma as well as other solid tumors. It can present in a similar fashion to other polyarthritides and may precede detection of the underlying malignancy[2–5]. In such cases recognition is critical for diagnosis and prompt treatment of the neoplastic process.

We describe a patient who presented with migratory asymmetric polyarthritis and was subsequently found to have advanced stage lung carcinoma. His joint pain was attributed to carcinomatous polyarthritis. Following the case report we present our learning objectives, which include the differential diagnosis of inflammatory polyarthritis, diagnostic approach to CP, and features that distinguish it from other more common causes of polyarthritis. We conclude with a brief discussion of the pathophysiology and management of CP.

CASE

A 43-year-old male presented with a 6-month history of migratory inflammatory asymmetric polyarthritis. He had seen his primary care physician on multiple occasions and been treated with nonsteroidal anti-inflammatory drugs (NSAIDS) and a several day course of low dose prednisone without relief. On presentation, he specifically complained of left ankle and left wrist pain, although he had previously experienced discomfort in both large and small joints including the left shoulder, right foot, right shoulder and elbow, and right knee. He stated the pain was worse in the evening and frequently kept him awake. He did not complain of any pain over the long bones. He also complained of recent sweats and fevers. He denied any weight changes. His past medical history was significant for coronary artery disease and peripheral vascular disease recently diagnosed during a routine preoperative evaluation for back surgery as well as a 90-pack-year smoking history. He had no history of sore throat, rash, diarrhea, or urethritis. There was no history of tick exposure. On physical exam, his temperature was 37.0, respirations 18, pulse rate 80, and blood pressure 129/64 mmHg. He was notably pale, mildly short of breath, and appeared to be in significant distress secondary to pain. The lateral metatarsal region of the left foot and left wrist appeared swollen and erythematous. Range of motion was severely limited secondary to pain. There was no clubbing noted. The rest of his physical exam was unremarkable. Complete blood count revealed a white cell count of 13.6 k/cumm, hemoglobin 10.4 g/dl, and platelets 439 k/cumm. A metabolic panel was significant for hyponatremia (119 mmol/l). Other electrolytes and renal function were within normal limits. Alkaline phosphatase was elevated at 431 IU/l, SGOT was 55 IU/l, and SGPT was 71 IU/l. Erythrocyte sedimentation rate (ESR) was 106 mm/h and c-reactive protein (CRP) 115 mg/l. C3 and C4 were elevated at 203 mg/dl and 47 mg/dl, respectively. Rheumatoid factor was 89 IU/ml. Antinuclear antibody and hepatitis serology were

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negative. An x-ray of the left wrist and both ankles showed no joint space narrowing, erosions, or periosteal reaction. Long bones were not imaged. Joint aspiration of the right ankle revealed moderate neutrophils (6–30 per high-powered field) without crystals. Gram stain and cultures were negative. He was started on prednisone 40 mg daily and naproxen 500 mg twice a day with only minimal relief of his symptoms. A chest x-ray showed a new left hilar mass. Computer-aided tomography of the chest showed hilar and mediastinal lymphadenopathy, left chest wall metastasis, and peritoneal carcinomatosis. Biopsy of a lymph node confirmed small cell lung carcinoma. Further imagining demonstrated diffuse osseous metastasis. His joint pain was attributed to carcinomatous polyarthritis. The patient received two cycles of cisplatinum plus etoposide with complete resolution of his arthritic symptoms. However, his overall health deteriorated, and he died weeks later.

DISCUSSION

Migratory polyarthritis is a common symptom encountered by primary care physicians. The differential diagnosis is broad and includes infectious causes, crystal induced arthropathy, rheumatoid arthritis, vasculitic syndromes, connective tissue disorders, and spondyloarthridies[6]. Less common etiologies include metastatic disease and paraneoplastic syndromes such as carcinomatous polyarthritis. The etiology of joint pain is often suggested by the history and physical. However, overlapping features of differing etiologies can complicate diagnosis. Our goal is to review the differential diagnosis of inflammatory polyarthritis before specifically discussing the diagnosis, pathophysiology, and treatment of CP.

Carcinomatous polyarthritis has been reported with a variety of solid tumors including lung, gastric, colon, breast, ovarian, laryngeal, and pancreatic (Table 1) [3–5,7–11]. The exact prevalence is unknown, but it is thought to be rare[4,12]. The age of onset generally reflects that of the associated malignancy. In our review including this case, patients ranged from 43–76 with a median of 61 years[3–5,7–11]. There does not appear to be a gender predilection. It has been reported to precede the diagnosis of cancer anywhere from 1 to 20 months, with most malignancies manifesting themselves within 3 months of joint symptoms[3–5,7–11].

Table 2. Differential Diagnosis of Migratory Polyarthritis

Palindromic rheumatoid arthritis
Crystal induced arthropathy
Reactive arthritis
Autoimmune disease (e.g., SLE, rheumatic fever)
Infectious polyarthritis (e.g., Lyme disease, chlamydia)

CP is a diagnosis of exclusion. Therefore, clinicians must be able to exclude other more common causes of polyarthritis presented in Table 2. Features suggestive of bacterial arthritis such as fever, abrupt onset, monoarthritis, purulent aspiration, and risk factors such as IV drug use, sexually transmitted diseases, immunosuppression, and/or extra-articular signs of infection are generally absent[6]. Although Lyme disease can present with an asymmetric polyarthritis, negative serum titers, a lack of exposure, and absence of other systemic symptoms can exclude this diagnosis[6]. Seronegative spondyloarthropathies such as reactive arthritis and enteropathic arthritis can usually be identified from the clinical history. Reactive arthritis generally occurs 1 to 3 weeks after an episode of urethritis or diarrhea secondary to Salmonella, Shigella, chlamydial, Yersinia, or Campylobacter infection[6]. Axial involvement is common with back pain and sacroillitis often observed. The most common peripheral joints involved are the feet, ankles, and knees. Other systemic signs include mucocutaneous lesions and uveitis[6]. Unlike CP, reactive arthritis responds to NSAIDs. Enteric arthritis is observed in association with inflammatory bowel disease (IBD). Our patient's history, sterile joint aspiration, and lack of response to NSAIDs argues against infectious and seronegative arthropathies. Crystal-induced arthropathies can be easily distinguished from CP by joint aspiration. Lack of crystals in our patient's joint aspirate excludes gout or pseudogout.

Hypertropic osteoarthropathy (HOA) is another paraneoplastic syndrome characterized by oligoarthritis, clubbing of the fingers and toes, and periostits of the distal ends of the long bones (2). It often affects knees, ankles, elbows, wrists, and metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. HOA is usually symmetric, painful, and can be associated with tenderness of the adjacent bones. Our patient

Table 1. Clinical Features of Carcinomatous Polyarthritis

Case report and (reference)	Type of neoplasm	Age/sex	Symmetric (S) vs. asymmetric (A)	Timing* (weeks)	Small joint involvement
Present case	Small cell carcinoma of lung	43 years/M	A	24	+
Stummvoll et al. [4]	Adenocarcinoma of colon	49 years/M	S	6	+
Eggelmeijer et al. [9]	Supraglottic squamous cell carcinoma	50 years/M†	S	44/52	+/+
Bennett et al. [10]	Adenocarcinoma of ovary	59 years/F	S	12	+
Madiedo JM et al. [7]	Non-small cell carcinoma	59 years/F	S	28	+
Pines et al. [5]	Breast cancer	60 years/F	S	14	+
Pines et al. [5]	Unknown primary	62 years/F	S	12	+
Pines et al. [5]	Oat cell carcinoma	68 years/M	S	6	+
Chuan et al. [8]	Tubular adenocarcinoma of stomach	68 years/M	S	80	+
Bradley et al. [3]	Spindle cell carcinoma	69 years/M	S	6	+
Stummvoll et al. [4]	Small Cell carcinoma of lung	70 years/M	S	4	+
Simon and Ford [11]	Adenocarcinoma Of colon	76 years/F	S	16	+

F=female, M=male
+ Positive, - negative
**Time period between arthritis symptoms and diagnosis of neoplasm*
†This patient presented with carcinoma polyarthritis twice

did not have any clubbing or tenderness over the long bones. Additionally, there was no periosteal reaction seen on joint x-rays. Thus, we did not feel HOA was the etiology of the arthritis.

Vasculitic syndromes, autoimmune disorders such as systemic lupus erythematous and rheumatic fever, and connective tissue disorders such as scleroderma and mixed connective tissue disorder can all have polyarticular involvement. However, CP lacks the other systemic manifestations that characterize these disorders, such as neurologic involvement, mucocutaneous lesions, claudication, Raynaud's phenomenum, renal involvement, gastrointestinal complaints, and associated antibodies such as ANA, anti-dsDNA, anti-Smith, anti-RNP, anti-centromere, and Scl-70. Our patient's lack of system involvement and negative ANA argued against a connective tissue disorder, vasculitis, or SLE. Rheumatic fever can also present as migratory arthritis, but is preceded by pharyngitis and accompanied by other systemic signs, such as carditis and erythema marginatum, which were absent in our patient.

In the absence of a known malignancy, CP can be difficult to differentiate from rheumatoid arthritis (RA). Peak onset of RA has been reported to be between 30–55 years of age; however, the incidence increases with increasing age, making the distinction between RA and CP particularly difficult in older populations. The arthritis in both conditions generally presents over the course of weeks to months[3–5,6,8–11]. In both conditions, patients commonly present with soft tissue swelling, limited range of motion of affected joints, and morning stiffness[3–6,8–11]. Features consistent with chronic disease and inflammation, including anemia, an elevated erythrocyte sedimentation rate and c-reactive protein, are often observed[3–7,11]. Several distinguishing features have been proposed.

Historically, CP has been characterized by late age of onset, acute onset, asymmetric joint involvement, a predilection for lower extremity joints, sparing of the wrists and hands, benign radiographic changes, and an absent rheumatoid factor[2,13–14]. However, our review showed the above observations are often not seen. In fact, in our review of 13 cases involving 12 patients, we noted symmetric joint involvement of the wrists and hands in 12 cases. Six of 13 cases had a detectable rheumatoid factor when reported[3–5,7–11]. The presence of rheumatoid factor in such cases can be partially explained by the underlying malignancy, which is associated with a positive rheumatoid factor in 10–20 percent of patients[13]. However, the number of positive cases we found exceeded the number expected with malignancy alone. Thus, features that have historically been used to differentiate between CP and RA are not always reliable. ANA was positive in 4 out of 13 cases we reviewed[3–5,7–11]. The joint fluid generally shows nonspecific inflammatory changes[2,3,11,13]. Radiographic studies are generally unremarkable with the exception of age-related changes[2,4,8,10]. The laboratory and radiographic findings in CP are summarized in Table 3.

CP responds to treatment of the underlying malignancy. In our review of 13 cases, 12 patients had resolution of symptoms after surgical resection and/or chemotherapy[3–5,7–11]. The return of arthritic symptoms can herald tumor recurrence[9]. Traditionally, the response to chemotherapy has been used to differentiate between CP and palindromic RA. This is not always reliable as chemotherapeutic agents have been used to treat refractory RA. However, our patients lack of previous episodes of migratory arthritis, failure to show any response to NSAIDs and prednisone, as well as the concurrent diagnosis of a malignancy make CP the more likely diagnosis. An additional means to differentiate these two disorders is a measaurement of anti-cyclic cytrullinated peptide antibodies. Anti-CCP has a similar sensitivity to RF (50–75%) with a higher specificity (90–95%). In early RA (3–6 months of symptoms) the sensivity of anti-CCP is 50–60 percent[15]. To our knowledge anti-CCP has not been reported in association with CP. An anti-CCP was not measured in our patient in light of his response to chemotherapy and cancer diagnosis.

The pathogenesis of this disorder is unknown. There has been much speculation about the possible role of circulating immune complexes (CIC), which have been observed in over 60 percent of some types of cancers[3]. Bennett et al. found elevated levels of a platelet-activating factor that disappeared with tumor resection and symptom resolution[10]. They postulated that this factor might be circulating immune complexes that are known to be platelet activators. The CIC could lead to a sterile inflammatory response if deposited in the synovium. Although they did not test for the presence of CIC, Bradley and Pinals failed to demonstrate immune complexes in immunofluorescent studies of the synovium in a patient with CP secondary to spindle cell carcinoma of the lung. Their failure to demonstrate immune complexes in addition to the rarity of CP relative to the overall presence of CIC suggests that additional factors play a primary role. Other proposed

Table 3. Laboratory and Radiographic Features of CP

Case report and (reference)	Rheumatoid factor	ANA	ESR (mm/h)	CRP (mg/dl)	Synovial fluid	X-ray
Present case	+	-	106	11.5	SI	N
Stummvoll et al. [4]	-	-	35	2.9	NP	STS
Eggelmeijer et al. [9]	-/-	-/-	30/53	NP	NP	MDC/MDC
Bennett et al. [10]	+	+	36/132	4+	NS	MDC
Madiedo et al. [7]	-	-	110	NP	N	N
Pines et al. [5]	-	-	NP	NP	NP	NP
Pines et al. [5]	+	+	95	NP	NP	NP
Pines et al. [5]	+	-	N	NP	NP	NP
Chuan et al. [8]	+	-	103	NP	NP	N
Bradley et al. [3]	-	+	107	NP	SI	STS
Stummvoll et al. [4]	-	+	53	4.6	NP	STS
Simon and Ford [11]	+	-	97	3.0	SI	NE

+Positive, -negative, STS=soft tissue swelling, SI=sterile inflammation, N=normal, MDC=minimal degenerative changes, NE=joint space narrowing and erosions, NS=nonspecific, NP=not performed

mechanisms include a cross reaction between tumor antigens and the synovium, disruption of 'antiarthritic' barriers by the tumor or immune response to the tumor, and an autoimmune phenomena involving lymphocytes originating in hyperplastic lymph nodes draining tumor sites[2,3,8,14]. Thus far, none of the proposed mechanisms has been substantiated.

Carcinomatous polyarthritis is a rare clinical entity associated with a variety of tumors. The differential diagnosis for CP is broad. CP is a diagnosis of exclusion. The history and physical can often distinguish CP from other more common causes of polyarticular arthritis. However, differentiating CP from RA can be quite challenging. This distinction is critical for prompt therapy of the malignancy. Often times CP does not fit into the presentation historically described. There are no definitive diagnostic tests, and ultimately clinical suspicion is the most important factor in accurate diagnosis. It should be suspected in patients with new onset of acute migratory arthritis at a relatively late age. The presence of rheumatoid factor and involvement of the wrists and hands should not lessen clinical suspicion, particularly in patients with risk factors for cancer. There are no clear recommendations for the extent of cancer screening in these patients. At the very minimum, age appropriate screening should be done. The treatment of CP is treatment of the underlying malignancy. The reemergence of arthritic symptoms should prompt an investigation for tumor recurrence.

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