Paraneoplastic arthritis — at the crossroads of rheumatology and oncology

Abstract. Paraneoplastic arthritides (PA) are a group of inflammatory arthropathies associated with latent or manifest malignancy, localized in a distant site in relation to the primary focus and caused by immune-mediated mechanisms. Although the pathogenesis of PA is unknown, immune-mediated mechanisms can cause paraneoplastic syndrome with a dominant feature of polyarthritis. Arthritis can be both the initial manifestation of the disease, and it can manifest itself some time before the oncological process. Common forms of PA include paraneoplastic oligo/polyarthritis; hypertrophic osteoarthropathy; remitting seronegative symmetric synovitis with pitting edema; palmar fasciitis and pancreatic panniculitis associated with pancreatic carcinoma. The purpose of this review article was to describe the clinical characteristics, diagnostic assessment and treatment of paraneoplastic arthritis, and highlight the challenges that healthcare professionals may face in order to distinguish these conditions from other autoimmune rheumatic diseases. Further research is needed to understand the mechanisms associated with PA and to develop new diagnostic biomarkers.

Keywords: paraneoplastic arthritis; polyarthritis; hypertrophic osteoarthropathy; palmar fasciitis; panniculitis

Introduction

Paraneoplastic arthritis (PA) is a group of inflammatory arthropathies associated with an induced or obvious malignant neoplasm that is localized in a distant place in relation to the primary focus and caused by immune-mediated mechanisms [1]. The term PA refers to a clinical syndrome characterized by joint pain, their swelling, and stiffness that may imitate other rheumatic diseases such as rheumatoid arthritis or spondylarthropathy. PA is not caused by the tumor masses themselves, metastases, metabolic abnormalities, or side effects of cancer treatment. Arthritis can be both the initial manifestation of the disease, and it can be detected some time before the oncological process [2]. Most often, paraneoplastic syndrome occurs in parallel with a malignant neoplasm. The prevalence of paraneoplastic rheumatic syndromes is 2.65 % [3]. There are no published studies devoted to the prevalence or frequency of PA itself.

Syndromes that meet the definition of PA include paraneoplastic oligo/polyarthritis, hypertrophic osteoarthropathy, remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, palmar fasciitis, and pancreatic panniculitis associated with pancreatic carcinoma. The aim of this literature review was to summarize the latest information on the above-mentioned syndromes, describing their clinical and laboratory features, approaches to the diagnosis and treatment, diagnostic approach and the treatment.

The literature review was compiled on the basis of electronic databases PubMed, MedLine and Scopus. Search keywords (“paraneoplastic arthritis”, “paraneoplastic polyarthritis”, and “paraneoplastic rheumatic diseases”) were used to identify the articles in English published up to November 2021. Sixteen large studies had been analyzed, including original studies, descriptive reviews, case series and case reports.

Paraneoplastic oligo/polyarthritis is a rare nosological form characterized by pain in the joints, swelling and the presence of synovitis during examination. The symptoms of paraneoplastic polyarthritis resemble manifestations of autoimmune rheumatic syndromes and may be the initial clinical sign of a malignant neoplasm. A series of cases of paraneoplastic polyarthritis showed that the patients were predominantly male, with a male to female ratio of 1.7:1 and had the average age of 54 years old [4]. Although several solid and hematologic malignancies have been associated with paraneoplastic polyarthritis,
Paraneoplastic arthritis is a form of paraneoplastic syndromes associated with lung cancer, lymphoma, leukemia, and myelodysplastic syndrome (Table 1) [4, 5].

In general, arthritic symptoms among the patients with malignant neoplasms can arise as a result of several mechanisms, including direct invasion of the tumor into the synovial membrane, soft tissue, or bone [6]. However, arthritis caused by synovial infiltration by leukemic cells does not belong to the group of paraneoplastic syndromes [22]. Despite the fact that the pathogenesis of paraneoplastic polyarthritis is unknown, immunological mechanisms are considered to play an important role. A report about the patient with oligoarthritis caused by renal cell carcinoma had demonstrated that tumor-specific T lymphocytes had infiltrated not only the carcinoma but also the synovial membrane, that was indicating cross-reactivity as a potential mechanism of paraneoplastic arthritis [23].

Conducted research had shown that arthritis can precede the diagnosis of a malignant neoplasm by a total of 10 months. However, it should be noted that both conditions can occur simultaneously with a wide range of symptoms [24]. Monoarthritis is a rare manifestation of paraneoplastic arthritis, but it can be the first manifestation with frequent localization in large joints, including the knee, shoulder, and elbow [5]. Most often, PA is manifested as oligoarthritis or polyarthritis, which is often diagnosed by mistake as peripheral spondyloarthritis or rheumatoid arthritis, which is manifested by pain, swelling of the joints with the presence of stiffness. With PA, both small and large joints can be involved in the process with symmetric or asymmetric manifestation. The main clinical characteristics of the patients with paraneoplastic polyarthritis include an old age, acute onset of the symptoms, asymmetric nature of joint damage, mainly damage to the joints of the lower limbs, and a high level of pain incompatible with the results of physical examination (Table 2) [25]. A rare clinical manifestation of PA is pain in the low back, more often associated with acute leukemia. Gur H. and co-authors [26] found that in 5.8% of the patients with acute leukemia an asymmetric arthritis of large joints and pain in the lumbosacral zone was developed, which is clinically very similar to spondyloarthritides.

Although the majority of the published clinical cases of paraneoplastic polyarthritis have been described as seronegative, there are case series of the patients with positive antibodies, including rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (ACCP) in the patients with PA [27–30]. Among this, a clinical case series showed that 27.2% of the patients with PA were seropositive according to the RF and 19% had antinuclear antibodies (ANA) in serum, although there is no information as for the antibody titers and their significance. ACCP were positive in 7 (10.7%) and RF in 15 (23%) of 65 patients with paraneoplastic polyarthritis [5]. Also, elevated levels of inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are quite understandable in the patients with paraneoplastic polyarthritis.

Unlike most of the patients with inflammatory arthritis, patients with paraneoplastic polyarthritis respond poorly to glucocorticoids (GC) and disease-modifying antirheumatic drugs [11]. Identification and treatment of the primary malignant neoplasm often leads to regression of joint symptoms. It is noted that in case of tumor recurrence after the treatment, PA does not recur [28, 29].

**Hypertrophic osteoarthropathy** is a form of paraneoplastic arthritis that is primarily associated with lung cancer [8]. This type of PA is characterized by drumsticks-like finger deformities, periostitis, and arthritis with a wide range of joint symptoms from polyarthralgia to severe symmetric polyarthritis with synovial effusion. There are 2 forms of hypertrophic osteoarthropathy: primary or idiopathic and secondary form. Several malignant neoplasms have been associated with secondary forms, such as lung adenocarcinoma, small cell lung carcinoma, lung metastases, and Hodgkin’s lymphoma (Table 1) [9]. Primary forms are caused by a non-malignant condition, such as chronic lung infections, some congenital heart defects, cystic fibrosis, and may be the main cause of hypertrophic osteoarthropathy [9].

<table>
<thead>
<tr>
<th>Paraneoplastic arthritis</th>
<th>Malignant neoplasms</th>
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<tbody>
<tr>
<td>Paraneoplastic oligo/polyarthritis [2, 4-7]</td>
<td>Lung cancer (the most common adenocarcinoma), hematological malignancies (lymphomas, leukemias, myelodysplastic syndrome), breast cancer, adenocarcinoma of the stomach and colon</td>
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<tr>
<td>Hypertrophic osteoarthropathy [8, 9]</td>
<td>Lung cancer (most common), lung metastases, Hodgkin lymphoma, nasopharyngeal cancer, esophageal cancer</td>
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<tr>
<td>Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome [10-13]</td>
<td>Cancer of the urogenital system (bladder, prostate, ovarian cancer), hematological malignancies (lymphoma, myelodysplastic syndrome, leukemia), gastrointestinal tract (colon, stomach cancer), lung cancer</td>
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<tr>
<td>Palmar fascitis and polyarthritis [14, 15]</td>
<td>Ovarian cancer (the most common), urogenital cancer (uterus, bladder, prostate), breast cancer, lung cancer, hematological malignancies (lymphoma, leukemia, multiple myeloma), gastrointestinal tract (pancreatic cancer)</td>
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<td>Polyarthritis and pancreatic panniculitis associated with pancreatic carcinoma [16-21]</td>
<td>Acinar cell carcinoma of the pancreas</td>
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The pathogenesis of hypertrophic osteoarthropathy remains poorly studied, and several hypotheses for their development have been proposed for today. Increased levels of vascular endothelial growth factor (VEGF) have been found in patients with hypertrophic osteoarthritis and lung cancer, as well as in patients with chronic hypoxia [31]. VEGF is a signaling protein that is involved in angiogenesis and belongs to the family of platelet-derived growth factor [32]. Increased production can be induced both by conditions associated with hypoxia, for example, bronchial asthma, and by malignant neoplasms, due to the mechanisms of tumor growth and metastasis [33]. Overexpression of VEGF by a tumor can cause vascular proliferation, edema, and the development of new bone tissue — signs that reflect the historical features of hypertrophic osteoarthritis [33].

Clinical signs of hypertrophic osteoarthropathy include joint pain, mainly in the knee, ankle, and metacarpal joints that is accompanied by noninflammatory exudation of joints and drumsticks-like deformity of the fingers, which are usually asymmetrical. The presence of drum-sticks during physical examination that is appearing within a short period of time should prompt the physician to evaluate the patient using imaging studies as for lung cancer [34].

The basis of the treatment for hypertrophic osteoarthropathy is a treatment of the main tumor and relief of the symptoms using analgesics such as nonsteroidal anti-inflammatory drugs. In some cases, bisphosphonates can be effective in the patients with refractory pain due to a decrease of VEGF level in plasma [35, 36].

Remitting seronegative symmetrical synovitis with pitting edema syndrome (RS3PE) is an inflammatory arthritis with a manifestation of unknown etiology in old age, which turns out to be synovitis, tendinitis, and swelling of both hands and less often the feet. RS3PE was described first in 1982 and can be different from rheumatoid arthritis by the absence of RF in plasma, rheumatoid nodules and erosions on radiographs [38]. Since the initial description of the disease, several case reports have demonstrated that RS3PE may be the first sign of latent neoplasia [10]. In a systematic review, Karmacharya P et al. [10] showed that in 16.31% of RS3PE patients (54 out of 331) a malignant neoplasm developed. In particular, malignant neoplasms of solid organs of the urogenital system (bladder, prostate, ovarian cancer) were the most frequent types of cancer, followed by hematological manifestations (non-Hodgkin’s lymphoma, myelodysplastic syndrome, leukemia, angioimmunoblastic T-cell tract (of colon, stomach cancer) and carcinoma of lungs (table 1) [10]. In addition, patients with a main tumor and RS3PE were more likely to require higher doses of GCs to reduce joint syndrome and more often had a relapse of the disease.

VEGF is involved in the process of pathogenesis of RS3PE, and elevated levels of VEGF may contribute to increased vascular permeability and synovial hypervascularization, leading to synovitis, flexor tenosynovitis, and soft tissue edema [12, 13]. Moreover, a small study of 6 patients with RS3PE and a solid tumor showed that the levels of interleukin 6 were elevated and immunosuppressive therapy led to a decrease in cytokine levels [39]. Radiographs of the hands in RS3PE are often unremarkable, and laboratory research may reveal elevated levels of ESR and CRP with negative RF and ACCP. The main goal of the therapy is to relieve symptoms with GC, and the treatment of the primary malignant neoplasm is considered to be important for clinical improvement.

Syndrome of palmar fascitis and polyarthrosis is a rare form of inflammatory arthritis that affects mainly women and is characterized by pain and swelling in small and large joints, thickening of the palmar fascia and flexion contracts, resembling Dupuytren’s contracts.

In the initial description of the syndrome in 1982 it was reported about 6 postmenopausal women with ovarian cancer who had palmar fascitis and polyarthrosis [40]. Although ovarian cancer remains the leading malignant neoplasm associated with palmar fascitis and polyarthrosis, some solid malignancies such as pancreatic, gastric, colon, lung, breast, or prostate cancer may also be associated with this symptom complex [40].

<table>
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<th>Table 2. Characteristic features that allow distinguishing paraneoplastic arthritis from rheumatoid arthritis</th>
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<td><strong>Clinical signs</strong></td>
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<tr>
<td>Age of disease onset</td>
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<td>Type of joint damage</td>
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<tr>
<td>Spread of joint damage</td>
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<tr>
<td>Rheumatoid nodules</td>
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<tr>
<td>Laboratory data</td>
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<td>X-ray data</td>
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<td>Response to glucocorticoids</td>
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<td>Features of the treatment</td>
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Notes. RF – rheumatoid factor, ACCP antibodies – antibodies to cyclic citrullinated peptides.
Although the pathophysiology of the syndrome remains unclear, immune-mediated mechanisms appear to play an important role, taking into account the presence of immunoglobulin and complement deposits in the palmar fascia [41]. Clinical features of the syndrome of palmar fasciitis and polyarthritis include symmetric polyarthritis of the hands, that is accompanied by synovitis, stiffness, and limited mobility of the fingers because of the rapid development of flexion contractures in both hands.

It is not surprising, that cancer antigen 125 (CA-125) associated with ovarian adenocarcinoma, was the most frequently elevated tumor marker in a series of 19 from 22 patients with syndrome of palmar fasciitis and polyarthritis [14]. Treating of the main tumor can relieve the symptoms of polyarthritis and stop the progression of palmar fibrosis.

Polyarthritis and pancreatic panniculitis associated with pancreatic carcinoma is a rare paraneoplastic syndrome and is manifested by joint pain and swelling, with frequent involvement of the ankle, knee, and wrist joints, accompanied by erythematous painful nodules on the skin, mainly, in the zone of the pretilial area, bones and knee joints. Abdominal pain may be absent, which complicates the diagnosis of the main malignant neoplasm [16, 17]. Pancreatic acinar cell carcinoma is the most common form of concomitant cancer of the pancreas, associated with polyarthritis and pancreatic panniculitis, and can be primary or ectopic (Table 1) [18].

An entry of elevated levels of pancreatic enzymes from the bloodstream into distant tissues, such as the synovial membrane and subcutaneous adipose tissue, can trigger peri-articular and subcutaneous adipose tissue necrosis, although the exact mechanism of the syndrome is unknown [18]. In addition, the release of free fatty acids from the periarticular tissues as a result of lipolysis into the joint space may contribute to joint inflammation and polyarthritis. Laboratory tests often show that elevated levels of pancreatic enzymes, including lipase, amylase, and liquid lipid crystals, may be present in the synovial fluid. Surgical treatment of acinar cell carcinoma remains the principle method of the treatment, and relief of the symptoms can be achieved with nonsteroidal anti-inflammatory drugs and GCs [16, 19].

Figure 1. Diagnostic approach of a patient with suspected paraneoplastic arthritis

Notes: ACCP – antibodies to cyclic citrullinated peptide, CT – computer tomography, Pap test – Papanicolau test, ultrasound – ultrasound examination.
Diagnostic assessment of paraneoplastic arthritis

It is extremely important to understand that malignant neoplasms can mimic various forms of inflammatory arthritis and can be the initial manifestation of the disease. Early recognition and treatment of cancer can have a beneficial effect on the outcome and improve the quality of life of the patients. The differential diagnosis of PA includes rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, systemic sclerosis, polymyalgia rheumatica, and viral infections such as hepatitis B and C [42]. The differential diagnosis with polymyalgia rheumatica deserves special attention because it is a pool of the patients that often overlaps: elderly patients with muscle weakness and joint pain and high level of laboratory activity. Evaluation of the patient begins with a thorough collection of his complaints and history, physical examination including chest and pelvic examination, and laboratory tests (Figure). Characteristic features that have been found on the initial evaluation can help to distinguish PA from other autoimmune rheumatic conditions, such as:

1. Elderly patients with polyarthitis and systemic complaints of fever, weight loss, and night sweats.
2. Patients with polyarthitis and warning signs of malignant neoplasm that is in the base, such as lymphadenopathy, drumsticks-like deformity of the fingers, and palmar contractures.
3. Elderly patients with persistent or treatment-resistant arthritis, for example, lack of response to moderate or high-dose of GC and/or disease-modifying antirheumatic drugs, negative immunological serological markers, and absence of characteristic features on radiographs.

Initial laboratory research should include clinical tests of blood and urine; determine the level of creatinine, liver function tests, hepatitis B and C serology testing and, also, chest and joint radiographs. The presence of anemia, thrombocytopenia, leukopenia, or significant leukocytosis, an increased average corpuscular volume of erythrocytes may indicate a possible hematologic malignant neoplasm, such as leukemia, lymphoma, or myelodysplastic syndrome. In addition, pathological changes in clinical blood analysis should prompt further investigation — iron and ferritin levels, peripheral smear, and electrophoresis of serum protein, flow cytometry, bone marrow and lymph node biopsy to establish the diagnosis of the main malignant neoplasm [42]. Levels of inflammatory markers, ESR and CRP may be elevated in patients with PA, but they are nonspecific and do not allow to distinguish rheumatic diseases from paraneoplastic syndromes. High titers of RF and ACCP can confirm the diagnosis of rheumatoid arthritis, although low titers can also be observed in patients with PA.

Radiographs of joints may be useful in the differential diagnosis for the evaluation of bone erosions and/or narrowing of joint spaces, data corresponding to rheumatoid arthritis or other inflammatory arthritis, but not excluding PA.

Of course, all patients should undergo age- and sex-appropriate cancer screening, including mammography, colonoscopy, Papanicolaou test (Pap test), prostate and thyroid examination, and X-ray of chest. Additional examination using imaging studies, such as computed tomography (CT) of the chest, abdomen, and pelvic organs, should be studied on a case-by-case basis. For example, patients at the age over 50 years old with iron deficiency anemia should undergo esophagogastroduodenoscopy, colonoscopy, and in the presence of chronic smoking (> 30 pack-years), the possibility of CT chest organs should be considered to do. CA-125 testing and transvaginal ultrasound can help to exclude ovarian cancer in the patients with palmar fasciitis and polyarthitis. In the presence of polyarthitis and pancreatic panniculitis, it is necessary to do a CT scan of the abdomen to exclude carcinoma of the pancreas.

Conclusions

Paraneoplastic arthritis is a group of inflammatory arthritides by malignant neoplasms, which can be disguised as systemic rheumatic diseases and demonstrate nonspecific symptoms. Increasing awareness of PAs associated with malignant neoplasms will help to make a diagnosis in time and improve outcome. To establish a diagnosis in the patients with PA, it is necessary to do a thorough collection of complaints and history, physical examination, laboratory and visual assessment. As it was noted earlier, treatment of the main malignant neoplasm can lead to the regression of the symptoms and improvement of the quality of life. Further research is needed for the development of biomarkers, autoantibodies, that allow to distinguish PA from other systemic rheumatic conditions and will provide a deeper understanding of pathogenesis of the disease and potential targets of the treatment.

References


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Огляді / Reviews

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Паранеопластичний артрит — на перехресті ревматології та онкології

Резюме. Паранеопластичні артрити (ПА) являють собою групу запальніх артропатій, асоційованих з прихованім або явним злоякісним новоутворенням, що локалізоване у віддаленому адякунтному місці щодо первинного вогнища в загальнокрілій системе. Такі артрити зазвичай виникають імунопосередкованими механізмами. Хоча патогенез ПА невідомий, імунопосередковані механізми можуть викликати паранеопластичний синдром з подушкоподібним набряком — поліартритом. Артрит може бути як початковим проявом захворювання, так і виявлятись за деякий час до маніфестації онкологічного процесу. Поширений відповідний шлях ПА включає ревматопластичний оліго-/поліартрит; гіпертрофічну остеоартропатію; ретінокулярну синдромічну синовіт з подушкоподібним набряком, при натисканні на який утворюється ямка; долонній фасційт; панкреатичний панікулит.

Ключові слова: паранеопластичний артрит; поліартрит; гіпертрофічна остеоартропатія; долонний фасційт; панкреатичний панікулит

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Ключові слова: паранеопластичний артрит; поліартрит; гіпертрофічна остеоартропатія; долонний фасційт; панкреатичний панікулит