EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2019.19145

Invited Review

Polyarthritis and its differential diagnosis

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Abstract

Polyarthritis is a term used when at least five joints are affected with arthritis. Several different diseases ranging from rheumatoid arthritis to infection diseases can lead to polyarthritis. Anamnesis, physical examination, laboratory findings and imaging methods are important tools to differential diagnosis.

Keywords: Polyarthritis, differential diagnosis, laboratory investigations

Introduction

Polyarthritis refers to a joint disease that involves at least five joints. One or more signs of inflammation, including pain, movement restriction, swelling, warmth, and redness, are seen in the joints involved. In the event that pain is the only symptom, it is difficult to differentiate polyarthritis from the causes of polyarticular joint pain (PJP), such as fibromyalgia or osteoarthritis. Imaging methods such as ultrasonography and magnetic resonance may be helpful in differentiating arthralgia from arthritis. Table 1 illustrates the diseases and their clinical characteristics that are frequently seen in clinical practice and cause non-inflammatory PJP.

In some cases, polyarthritis can be severe enough to necessitate the admission of patients to emergency services, or it can be asymptomatic and may remain undiagnosed for months. Several diseases ranging from rheumatic arthritis (RA) to infectious diseases can lead to polyarthritis. Anamnesis, physical examination, laboratory findings, and imaging methods are the tools that support an accurate diagnosis. Herein, we aimed to underline the differential diagnosis of a patient with polyarthritis and in doing so, contribute to clinical practice.

Clues for differential diagnosis

Demographic data: Age and gender itself may narrow the potential diagnostic options. For example, in a young male patient, systemic lupus erythematous (SLE) is at the last position on the list of differential diagnoses of polyarthritis. The incidence of crystal arthropathy is higher in older patients. The other diseases of advanced age, such as polymyalgia rheumatica and giant-cell arthritis, can also be the causes of polyarthritis.

History: Diseases associated with connective tissue disorders such as Raynaud's phenomenon and xerophthalmia, psoriasis, inflammatory back pain, symptoms of inflammatory bowel disease, viral infection, infectious diarrhea, and genitourinary infection should be checked in each patient. Chronology of the onset of symptoms is crucially important in defining the problem.

Genetic susceptibility: Polyarthritis is not a common sign of auto-inflammatory diseases, the Mendelian-inherited prototype of which is Familial Mediterranean Fever (FMF). Rather, Rheumatic diseases accompanied by polyarthritis are associated with multifactorial susceptibility. Family history is can only be a matter of fact in ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Classification of polyarthritis: If polyarthritis limits itself in less than 6 weeks, it is defined as acute polyarthritis; if the symptoms last longer than 6 weeks, then chronic polyarthritis is suspected. While acute polyarthritis is frequently associated with viral infections, RA is one of the most likely diagnoses in chronic polyarthritis. The types of joints involved and their symmetric involvement can be considered as loadstars. It is defined as symmetric arthritis if at least half of the joints involved are symmetric. Involvement

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Cite this article as: Alpay-Kanıtez N, Çelik S, Bes C. Polyarthritis and its differential diagnosis. Eur J Rheumatol 2019; 6(4): 167-73.

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Submitted: July 29, 2019
Accepted: August 13, 2019

Table 1. Causes and clinical features of polyarticular joint pain.

	Sex	Age	Accompanying findings	Laboratory
Fibromyalgia	F>>M	30-55	Fatigue and sleep disturbances, cognitive disturbances, psychiatric symptoms, headache, paresthesia	None
Osteoarthritis	F>M	>60	Pain is worse with joint use, bony swelling, joint deformity uch as Heberden's nodule	None
Osteomalasia	F=M	nr	Muscle weakness, spasms and cramps, difficulty walking, fracture	Increased ALP, PTH; reduced Ca, P, 25-hydroxy vitamin D
Thyroid dysfunction	F>M	30-55	Palpitations, sweating, weight loss, hair loss	Abnormalities of TSH, sT4
Hyperparathyroidism	F>M	>60	Weakness and fatigue, polyuria, polydipsia, osteoporosis	Increased PTH, Ca; reduced P
Hypermobility syndromes	F>M	<30	Recurrent joint subluxations, hyperextensible skin, bowel symptoms	None
Malignancies	F=M	nr	Weight loss, fever, pain at rest and at night	Hypercalcemia, increased LDH, cytopenia

F: Female, M: Male, nr: Specific age range not reported, ALP: Alkaline phosphatase, PTH: Parathyroid hormone, TSH: Thyroid stimulating hormone, Ca: Calcium, P: Phosphorus, LDH: Lactate dehydrogenase

Table 2. Clinical features of common rheumatic diseases causing polyarthritis.

	Age			Sex		
	<40	40 -60	>60	Female	Male	Classification of polyarthritis
Rheumatoid arthritis	+	+++	++	++	+	Mainly affects small joints, symmetric, additive
Psoriatic arthritis	+++	+++	+	++	++	Affects small, large, axial joints, asymmetrical, additive
Ankylosing spondylitis	+++	++	+	+	++	Mainly affect large joints, asymmetrical, additive
Reactive arthritis	+++	++	+	++	++	Mainly affects large joints, asymmetrical, migratory
Crystal arthropathy	+	++	+++	++	+	Mainly affects small joints, asymmetrical, intermittent
Systemic lupus erythematosus	+++	++	+	++++	+	Mainly affects small joints, symmetrical, additive
Systemic vasculitis	++	+++	++	+++	++	Mainly affects small joints, symmetric, additive.

of large joints such as knee and ankle accord more with spondyloarthropathy (SpA), whereas symmetric involvement of small joints of the hand is expected in RA or SLE. Detection of axial system involvement is important, as it narrows the differential diagnosis down to the SpA group. There are usually three major patterns of joint involvement.

Main Points

- Polyarthritis can be a clinical manifestation of distinct disease processes and the differential diagnosis is reasonably very broad.
- Rheumatic diseases, which prototype is rheumatoid arthritis, cause polyarthritis as well as non-rheumatic diseases such as infectious diseases, malignancies and even some medications.
- A good anamnesis and physical examination are the main pillar of the differential diagnosis of polyarthritis.

Migratory: At the onset of arthritis, initially only one or more joints are involved, which they improve completely after several days. Following this, another joint region is involved, and in this way, polyarthritis occurs gradually. Acute rheumatic fever (ARF) is a typical example of this pattern of arthritis.

Additive: Joints become involved within days or weeks. This may be a potential pattern for PsA.

Intermittent: Polyarthritis attacks continue for a while, following which complete improvement occurs. Polyarthritis recurs after a while and may progress in this way in adult patients with adult Still's disease (ASD).

As a result, polyarthritis is classified according to the following parameters (1);

1. Duration: Acute or chronic?
2. Type of affected joints: Large or small; with axial involvement or not?
3. Type of involvement: Symmetric or asymmetric?
4. Clinical pattern: Migratory, additive, or intermittent?
5. Table 2 illustrates the characteristics of common rheumatic diseases presenting with polyarthritis.

Physical examination

Physical examination would provide support to the diagnosis as per the following basic points:

Classification of polyarthritis: In light of information obtained via anamnesis; classification of polyarthritis is completed by physical examination. Accompanying extra-articular musculoskeletal system involvement such as enthesitis and tenosynovitis can be determined as well. It can be said that enthesitis and tenosynovitis are seen more prominently than the SpA group or seronegative diseases. Any limitation in the range of motion and detection of specific deformities is crucial. For

example, irreducible swan neck deformity is always a sign of RA.

Accompanying findings: Detecting the systemic symptoms accompanying polyarthritis during physical examination and evaluating them accurately is important. Meanwhile, information about the diseases that might be the extra-rheumatic causes of polyarthritis can be obtained as follows;

Weakness, weight loss, fever: Severe polyarthritis may cause weakness and weight loss due to intensive inflammation. In the presence of accompanying weakness and weight loss, systemic rheumatic diseases such as SLE and systemic vasculitis, which may possibly involve the visceral organs, should be at the top on the list of differential diagnoses. Fever may occur along with this inflammation. Only the presence of fever would require frequent questioning, primarily to rule out infectious diseases, lymphoproliferative diseases, and malignancy.

Skin and mucosa: Presence of specific skin lesions such as malar rash, vasculitis rash, and psoriasis are important in making the diagnosis. Raynaud's phenomenon can be detected during physical examination. There may be specific cutaneous signs of the infectious diseases, primarily in viral infections. Figure 1 illustrates palmoplantar skin rash in a syphilis patient with polyarthritis. Inspection of the mucosa should be a part of the physical examination. For instance, presence of an ulcer in the oral mucosa of a young female with polyarthritis may support the diagnosis of SLE. Genital aphthae that accompany recurrent aphthous lesions may be enough proof to make a diagnosis of Behçet's Disease.

The eye: It is important to identify the characteristics of uveitis determined during the ophthalmological examination. While anterior uveitis accompanies SpA group diseases, pan uveitis or posterior uveitis can be the signs of Behçet's Disease (2). Uveitis with granulomatous features is significant in tuberculosis and sarcoidosis. Infectious etiology is likely to be more important if retinitis is determined. It is less likely for episcleritis to accompany a systemic disease, whereas scleritis can be a sign detected concurrently with polyarthritis in patients with systemic vasculitis (3). Dry eye is one of the diagnostic criteria of Sjogren's syndrome, which is among the causes of polyarthritis.

Reticuloendothelial system: Peripheral lymphadenopathy can be easily detected via physical examination. In such case, the possibility of a lymphoma must be excluded. SLE, ASD, and Sjogren's syndrome are the rheumatic diseases that cause lymphadenopathy. Hepatosplenomegaly can be found in ASD or SLE; however, it is more likely to be an indicator of lymphoproliferative disorders than lymphadenopathy.

The lungs: In a patient with polyarthritis, pulmonary findings can either be in the form of pulmonary involvement of systemic rheumatic disease, associated with infectious disease, or related to a malignancy. Pulmonary signs likely to be seen in rheumatic diseases, such as pleuritis, pleural effusion, airway disease, lung nodules, interstitial lung disease, pulmonary hypertension, and pulmonary hemorrhage, must be examined in detail both in the physical examination and in the anamnesis (4). Detection of lung nodules may require histopathological examination to exclude malignancy from the differential diagnosis.

Cardiovascular system: ARF can be encountered in adulthood even though it is an uncommon cause of polyarthritis in this age group. In such a case, cardiac murmur that is detected on physical examination can be a sign of cardiac valve involvement. Examination of peripheral pulses is important to suspect aortitis. Polyarthritis can be encountered rarely in Takayasu arteritis or in giant-cell arteritis (5). Infective endocarditis must be considered in the differential diagnosis in a polyarthritis case with new-onset fever and cardiac murmur. Syphilis could be the cause of polyarthritis in a patient with advanced-stage aortic insufficiency. Aortic dilatation and related aortic insufficiency may develop in AS (6). Pericardial effusion and myocarditis, the signs that might accompany rheumatic diseases, are suspected during physical examination.

Gastrointestinal system: Dysphagia may be suggestive of scleroderma or polymyositis. Infectious diarrhea is one of the most important causes of reactive arthritis. Peritonitis can be a sign of SLE or FMF. Diarrhea or perianal disease may be suggestive of inflammatory bowel disease. Signs of mesenteric ischemia could be associated with systemic vasculitis, particularly in emergency clinics. Abdominal collaterals may be the signs of Budd Chiari syndrome in a patient with Behçet's Disease.

Urogenital system: In a polyarthritis patient with accompanying kidney failure, SLE and systemic vasculitis would be at the top of the list of differential diagnoses. Detection of proteinuria and hematuria, which indicate glomerular involvement, is important. Urogenital infections can be the causes of reactive arthritis (7). Epididymitis and orchitis, which might be the signs of systemic vasculitis, can be detected on physical examination.

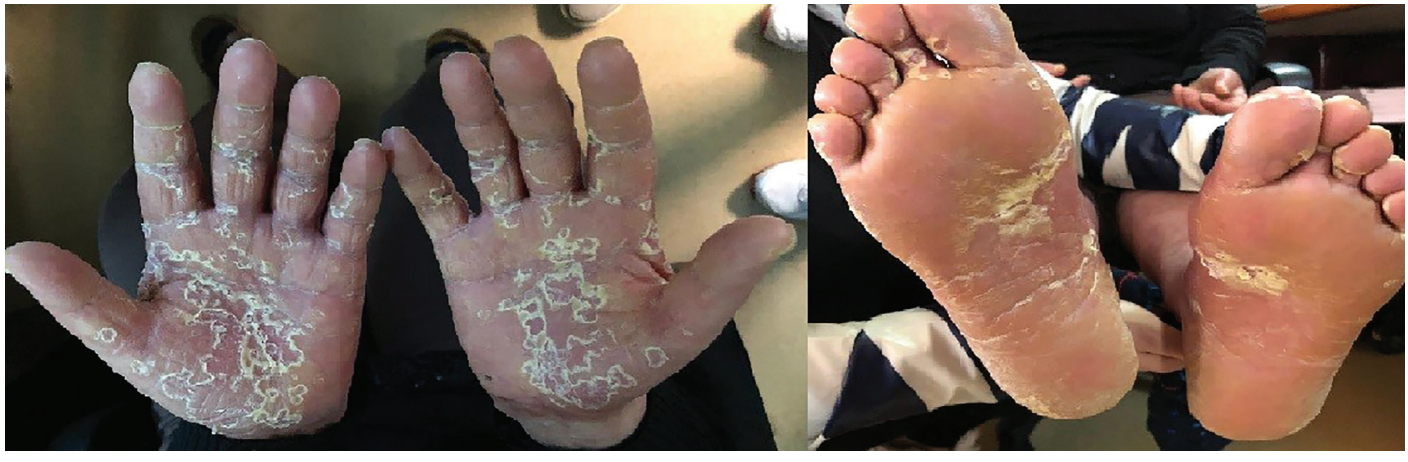

Figure 1. Palmoplantar skin rash in a syphilis patient with polyarthritis.

Nervous system: Motor or sensorial loss can occur due to peripheral nerve involvement. Observing a drop foot due to mononeuritis multiplex as the patient walks into the examination room suggests systemic vasculitis. Signs such as side weakness, increased deep tendon reflex, ataxia, and dysphagia due to central nervous system involvement can be detected on physical examination. Neurological examination, in detail if necessary, should be a part of the general rheumatologic examination.

Laboratory findings

Laboratory findings are the third most important component of differential diagnosis after a detailed anamnesis and physical examination. Even simple laboratory tests may give clues in making a differential diagnosis.

Complete blood count: Cytopenia is a supportive finding for SLE. However, polyarthritis can be one of the components of the clinical manifestation of leukemia and lymphoma that causes cytopenia. Lymphocytosis is a valuable finding for chronic lymphoproliferative disorders. Polycythemia and thrombosis raise doubts on myeloproliferative disease as well. Presence of eosinophilia can be a sign of Churg-Strauss vasculitis and hyper eosinophilic syndrome with polyarthritis.

Urinalysis: A simple urinalysis can be helpful for making several differential diagnoses. The presence of pyuria may indicate polyarthritis reactive to a urinary system infection. The presence of proteinuria and/or hematuria is quite valuable for SLE and systemic vasculitis, which has the potential to involve glomeruli and may require a renal biopsy to make the diagnosis.

Acute phase reactants (APR): These are the proteins whose serum concentrations increase due to inflammation and tissue injury. C-reactive protein (CRP) is one of the most common APRs. Erythrocyte sedimentation rate (ESR) is an indirect method to measure APR and is frequently used in clinical practice (8). Serum amyloid A, complement components, alpha-1 antitrypsin, fibrinogen, hepcidin, ferritin, and haptoglobin are the other APRs. Increased APR is not always a sign of rheumatic disease. Infectious diseases and malignancies (rarely) can increase APRs. The inflammation in SLE is not expected to elevate CRP, except in some exceptional cases. Although APRs are usually elevated in patients with rheumatic disease-related polyarthritis, they sometimes are within the normal limits. Normal APRs do not exclude the diagnosis of polyarthritis or rheumatic disease. Very high ferritin levels may be a supportive sign of ASD, but ferritin is not increased in a small proportion of ASD patients (9).

Other biochemical tests: Uric acid should be studied in every patient with suspected crystal arthropathy. Uric acid concentration can be normal in a small proportion of patients with gout arthritis or during an acute attack of gout. Liver and kidney function tests should be considered in every patient with polyarthritis. SLE and systemic vasculitis patients can present with acute kidney failure. Acute hepatitis or other viral agents can compromise hepatic function tests. Elevated lactate dehydrogenase (LDH) is suggestive of autoimmune hemolytic anemia, ASD, myositis, and malignancy. Elevated creatinine kinase should be evaluated in every patient with polyarthritis and may be a potential indicator of myositis.

Autoantibodies: They are critical in the diagnosis of RA, SLE, other connective tissue diseases, and systemic vasculitis. Rheumatoid factor (RF), anti-CCP antibody, and antinuclear antibody (ANA) should be studied in each patient with polyarthritis. Based on accompanying symptoms, endonuclear antibody (ENA) panel and anti-neutrophil antibody (ANCA) can also be studied. RF may be positive in RA, in SLE or other connective tissue diseases, and in systemic vasculitis. RF may be positive in patients with infectious diseases and malignancies (10). It is important to establish anti-CCP positivity to make a diagnosis of RA. High-titer positivity has high specificity in diagnosing RA (11). Accurate interpretation of the result of ANA testing is also important, where attention needs to be paid to the titer and pattern. Low-titer ANA positivity can be seen in about 30% of healthy females. ANA can also be positive in other autoimmune diseases or malignancy (12). If ANA is positive, ENA panel, anti-DNA antibody, and complement testing can be performed. Sensitivity of anti-DNA ranged from 27.7% to 100%, while its specificity ranged from 13% to 89.1% (13). In a polyarthritis case with negative ANA testing, there is usually no need to study further tests including ENA panel, anti-DNA antibody, and its complement.

Viral and bacterial serology: It is not a routine examination in polyarthritis patients but can be studied to support the diagnosis in case of clinical suspicion.

Synovial fluid analysis: Synovial fluid analysis, which is critical in diagnosing monoarthritis, has a limited role in the differential diagnosis of polyarthritis. Detecting crystals in the synovial fluid of the patients with crystal arthropathy is diagnostic. Microscopic examination and synovial fluid culture be necessary if polyarthritis is caused by the direct invasion of an infectious agent, such as tuberculosis and leprosy.

Radiological methods

Radiography can make a substantial contribution to the diagnosis of polyarthritis. Hand radiography is valuable in making a diagnosis of RA and PsA. Erosion and lytic lesions can be diagnostic for RA. Presence of sacroiliitis can be demonstrated radiographically by a suprapubic sacroiliac radiograph. Sacroiliac magnetic resonance imaging (MRI) is performed in case of suspected sacroiliitis despite the availability of a normal X-ray. Linear calcifications of cartilage detected in the knee radiography can support the diagnosis of pseudogout. No doubt, lung radiography must be performed in patients with respiratory system symptoms. Ultrasound, MRI, X-ray, CT, and PET-CT are potential radiological methods of diagnosis.

Ultrasonography (US) can be used to evaluate the severity and make the differential diagnosis of arthritis. Detecting enthesopathy and tendinopathy via US is significant for SpA (14). Starry sky appearance in the joints of patients with crystal arthropathy is helpful in making the diagnosis. Use of US also a valuable tool in clinical follow-up to monitor treatment efficacy. Temporal artery doppler US findings can help with differential diagnosis in case of clinical suspicion.

Contribution of computed tomography (CT) and MRI to the diagnosis of polyarthritis is limited, except for SpA. However, they can be used for the differential diagnosis of accompanying system involvements. For example, thoracic CT findings are quite valuable in interstitial lung disease. In addition, if arthritis is suspected, MRI may be helpful in demonstrating synovitis.

PET-CT is helpful in making a differential diagnosis in cases with suspected malignancy. Recently, it was understood that PET-CT contributes to the differential diagnosis of large vessel vasculitis. Large vessel vasculitis is a rare cause of polyarthritis (5).

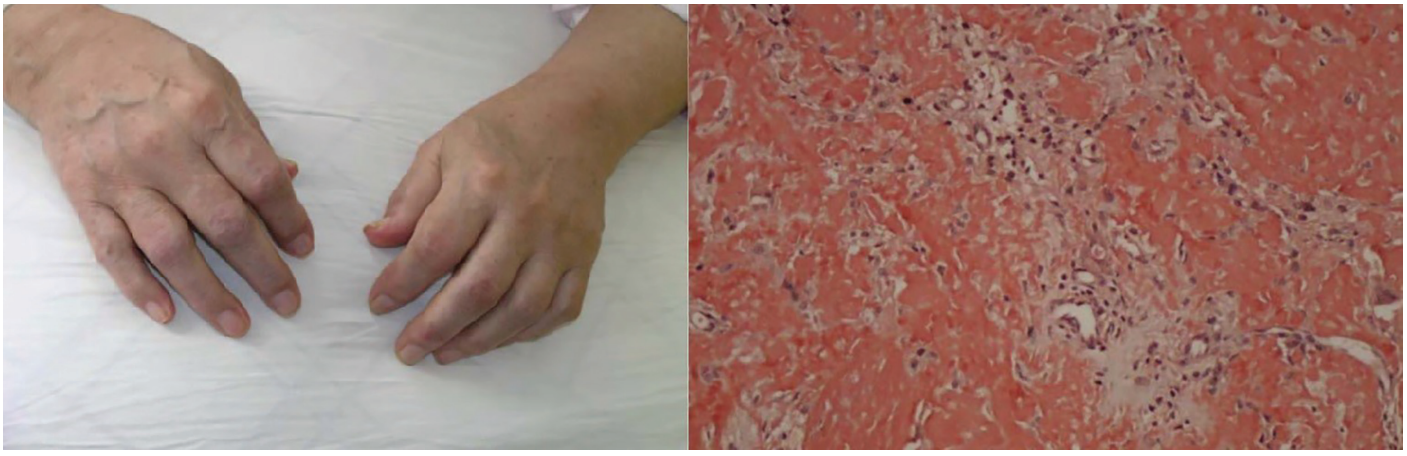

Figure 2. Symmetrical enlargement of wrists and proximal interphalangeal joints. Her percutaneous synovial biopsy with amyloid deposits confirmed by Congo red staining. Hematoxylin-eosin staining; original magnification 640.

Table 3. Causes of polyarthritis.

Inflammatory rheumatic diseases	Rheumatoid arthritis
	Psoriatic arthritis and other spondyloarthropathies
	Crystal arthropathies
	Systemic lupus erythematosus
	Sjogren's syndrome, scleroderma and other connective tissue disorders
	Systemic vasculitis, sarcoidosis, Behcet's disease etc.
Infective disorders	*Invasive joint infections*
	I-Viral infections (Chikungunya, HIV, HCV, HBV, human parvovirus B19 etc.) ii.
	II-Bacterial infections (staphylococcal, gonococcal, meningococcal, Brucella, Borrelia [Lyme arthritis], leprosy arthritis etc.)
	Reactive arthritis (Infections without joint invasion)
	I-Sexually acquired (Chlamydia trachomatis, Ureaplasma)
	II-Enterocolitis (Campylobacter, Salmonella, Shigella, Yersinia)
	III-Others (Infective endocarditis, rheumatic fever, poststreptococcal reactive arthritis)
Malignancies	Solid tumors (lung, breast, urinary bladder, prostate cancer etc.)
	Hematologic malignancies (leukemia, lymphoma, myelodysplastic syndrome, multiple myeloma)
Drugs	Antimicrobials (tetracyclines, quinolones, rifampicin, voriconazole)
	Anti-diabetic DPP-4 inhibitors (sitagliptin, linagliptin, alogliptin)
	Chemotherapeutics [aromatase inhibitors (anastrozole, letrozole), taxanes (paclitaxel, docetaxel and cabazitaxel)]
	Immune check point inhibitors
	Psychotropic 5-HT2A antagonists (mianserin, mirtazapine, nefazodone)

Histopathology

Synovial histopathology is infrequently required in polyarthritis. Figure 2 demonstrates a polyarthritis case diagnosed with primary amyloidosis via synovial biopsy. Histopathology is rather important for making the differential diagnosis of accompanying symptoms or in evaluating visceral organ involvement.

Extra-rheumatic causes of polyarthritis

Whether acute or chronic, polyarthritis can have different causes other than rheumatic diseases. These possibilities make the internal medicine perspective even more important in the evaluation of patients with polyarthritis (Table 3).

Infectious diseases: Numerous different bacteria, viruses, fungi, and parasites can cause

polyarthritis. Infections may lead to polyarthritis over three different mechanisms (15);

1. Direct invasion: A microbiological agent directly infects the synovial tissue. This is causes monoarthritis but may lead to polyarthritis in rare cases (e.g. Syphilis, leprosy).
2. Immune-mediated inflammation: Antimicrobial antibodies lead to polyarthritis due to the similarities between microbiological antigens and autoantigens (e.g. ARF, Lyme disease).
3. Reactive arthritis: Urogenital or gastrointestinal system infections can cause inflammatory joint diseases like spondyloarthritis, but the microbiological agent is not detected in the synovial fluid.

It is unnecessary to perform a serological examination for overall potential microbiological agents in every patient with polyarthritis. However, as was mentioned above, culture and antibiogram testing or serological examination is performed if the evaluation of accompanying symptoms suggests a case of infectious polyarthritis. For this reason, a good rheumatologist needs to know the clinical manifestations of infectious diseases and request for an infectious diseases consultation whenever necessary.

Malignancies and polyarthritis: Polyarthritis can usually occur concurrently with malignancies as a paraneoplastic syndrome. Tumor antigen-related circulating immune complex-mediated antibodies or cross antibodies are deemed responsible for the pathogenesis, however, the exact pathogenesis remains unknown. Paraneoplastic polyarthritis is more common in males (1.7:1) and peaks between the ages of 50 and 60 years (16). About one third of the overall cases had a hematolymphoid malignancy, whereas adenocarcinomas of the lung and breast were the most prevalent solid tumors. This type of arthritis is usually of sudden onset accompanied by high levels of inflammatory markers, such as CRP and ESR (17). Of all patients with paraneoplastic arthritis, only 27.2% are positive for RF and 19.0% are positive for antinuclear antibodies. Less frequently, anti-CCP antibodies can be positive (18). It is unnecessary to screen all patients presenting with polyarthritis for malignancy, but further analyses should be performed in the presence of weight loss, lymphadenopathy, etc.

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE): It is a form of polyarthritis that occurs in the elderly. It is characterized by the symmetrical involvement of small joints and marked pitting edema on the dorsum of the hands and feet, a sudden inflammatory onset, RF negativity, and an overall excellent prognosis. Prevalence of malignancy is increased in RS3PE, thus, the patients diagnosed with RS3PE need to be evaluated for malignancy.

Drugs and polyarthritis: Polyarthritis patients should be questioned in detail about the medications they have been receiving. There has been an increasing amount of data in recent years suggesting that immune checkpoint inhibitors targeting PD-1 (nivolumab, pembrolizumab), PD-L1 (durvalumab), and/or CTLA-4 (ipilimumab, tremelimumab), which have been increasingly become popular in recent years, can cause polyarthritis (19). There are case reports that show that antibiotics such as clindamycin, and other medications such as anti-thyroid drugs, can cause polyarthritis (20).

Conclusion

Systemic evaluation is essential for making a differential diagnosis in a patient with polyarthritis. Anamnesis should be target-oriented and obtained proficiently, a detailed physical examination should be performed and, thereafter, possible differential diagnoses should be identified. It is an optimistic approach to expect that the definite diagnosis can be obtained via laboratory tests before making a differential diagnosis using anamnesis and physical examination. It should be kept in mind that not only rheumatic diseases but also infectious diseases, malignancies, and even some medications may cause polyarthritis. In addition to simple laboratory tests, RF, Anti-CCP, and ANA are adequate for baseline antibody analysis in a patient with polyarthritis. More detailed laboratory tests or antibody analyses should be performed in patients, but only if it is necessary.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.A.K., S.Ç., C.B.; Design - N.A.K.; Supervision - S.Ç., C.B.; Resource - N.A.K.; Materials - N.A.K.; Data Collection and/or Processing - N.A.K.; Analysis and/or Interpretation - N.A.K.; Literature Search - N.A.K.; Writing Manuscript - N.A.K.; Critical Review - S.Ç., C.B.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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