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Letter to the Editor

Myeloma-associated amyloid arthropathy masquerading as seronegative arthritis

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Dear Editor,

Multiple myeloma, a clonal B-cell neoplastic disorder, is characterized by the proliferation of atypical plasma cells. Patients with multiple myeloma present with anemia, fractures, lytic lesions in the bones, and renal failure.[1] Both small and large joints have been reported to be involved, and it is difficult to differentiate from other polyarthritis such as seronegative rheumatoid arthritis (RA), psoriatic arthritis, and reactive arthritis.[2] Amyloid deposits comprise light chains in beta-pleated sheets.[1] The joint involvement in multiple myeloma occurs due to amyloid deposition and is referred to as myeloma-associated amyloid arthropathy (MAA). It is essential to differentiate MAA from these, as their treatments differ, and it is important to identify multiple myeloma as the underlying malignancy. We report two cases of MAA, the former case diagnosed years after long-standing seronegative RA and the latter, initially presenting as fibrosing tenosynovitis and later diagnosed with systemic amyloidosis with multiple myeloma.

A 60-year-old female who was a known case of seronegative RA was in follow-up in the rheumatology clinic at our center for 9 years. She developed progressive swelling, tenderness, and decreased movement of Proximal interphalangeal (PIP), Distal interphalangeal (DIP) joints, wrists, elbows, shoulders, knees, and ankles. She complained of generalized weakness, decreased appetite, difficulty in swallowing, macroglossia, and bilateral pitting edema. Her husband also noticed some purple-colored patches over the scalp. She had carpal tunnel syndrome of the right wrist for which she underwent median nerve decompression. She was worked up in line of amyloidosis. The abdominal fat pad biopsy was negative. Laboratory investigations are summarized in Table 1. Although the patient's bone marrow examination demonstrated 20% plasma cells, her serum immunofixation was positive for lambda light chain, and the kappa/lambda ratio was altered (0.009). Synovial biopsy from the right knee joint was suggestive of amyloid deposits [Figure 1a]. Thyroid function tests were normal. Echocardiography of the heart was suggestive of severe pulmonary arterial hypertension. She was started on decongestants from the cardiology team. X-ray of the hands and knees showed periarticular osteopenia and soft-tissue swelling. Radiological screening of the skeleton did not show any lytic lesions. Her final diagnosis was concluded as multiple myeloma with associated amyloid arthropathy. She was initially treated with thalidomide and dexamethasone, but in view of nonimprovement in symptoms, the patient was shifted to bortezomib and dexamethasone regime. Arthritis improved significantly after 8 weeks of therapy with reduction in swelling, tenderness, and improvement in mobility. However, poor cardiac status continues to cause limitations of her daily activities.

The second case was that a 34-year-old female was admitted with complaints of multiple joint swelling involving the knees, ankles, shoulders, wrist, and small joints of the hand which gradually progressed over 1 year [Figure 1b]. She had limited mobility, difficulty in performing daily activities, generalized weakness, loss of appetite, and weight loss. At the time of presentation, 1 year back, she was admitted with acute renal

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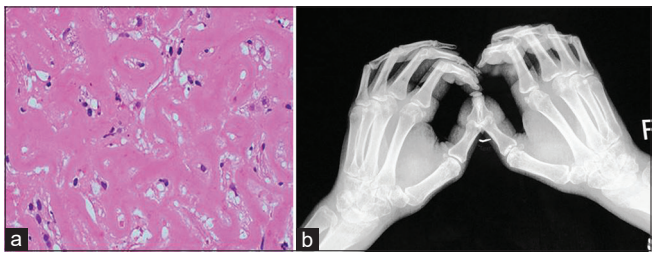

Figure 1: (a) Case 1 - Synovial biopsy section showing amorphous eosinophilic acellular material in the fibrocollagenous tissue along with mild mononuclear cell infiltrates and synoviocytes. (b) Case 2- X-ray of the hands showing joint deformities

failure and arthritis. Due to marked edema and new-onset hypertension, the nephritic syndrome was thought of but urine failed to show active sediment on numerous occasions. Her laboratory investigations are summarized in Table 1. Her ANA, ANCA, and RA screen and complement levels were in the normal range. Viral markers were negative. A diagnosis of fibrosing tenosynovitis was made, and she was started on steroids by the rheumatology team. Since she developed acute psychosis due to steroids, they were tapered and stopped. Her joint symptoms improved transiently but symptoms started worsening about 6 months later during the course of the illness. Physical examination revealed that the patient was cachexic. There was bilateral pedal edema. Joint examination revealed swelling and tenderness of bilateral PIP, Metacarpophalangeal (MCP) joint, wrists, knees, ankles, and shoulder joints. There was no other remarkable finding on systemic examination. Biopsy from the MCP joint confirmed the presence of amyloid deposits with special Congo red stain. The patient was diagnosed to have amyloid arthropathy, secondary to multiple myeloma. She was started on bortezomib, cyclophosphamide, and dexamethasone chemotherapy following which there was a significant improvement in her symptoms.

MAA resembles inflammatory arthritis with juxta-articular soft-tissue swelling, mild periarticular osteoporosis, subchondral cystic lesions, and well-defined sclerotic margins.[3] The incidence of MAA in plasma cell dyscrasias has been estimated between 3.7% and 9.2%.[4,5] It is an immune-mediated entity, with predominant role of macrophage-associated inflammasomes, causing release of interleukin-1 beta and related cytokines in the synovial membrane.[6] MAA is usually of two types. If amyloid is deposited around the joint tissues and synovia, the clinical picture resembles RA affecting small joints. When amyloid deposition occurs in the bone marrow usually affecting the bigger joints (e.g., hip joint, shoulder joint, etc.) patients present with fractures.[7]

Majority of cases present as symmetrical polyarthritis and are misdiagnosed and treated as cases of RA for many years till the symptoms start becoming extremely debilitating. In a case series of 101 patients with MAA, arthritis was the presenting manifestation in 63 patients and it preceded the diagnosis of myeloma by 1–84 months. Thirty-three cases were mistreated as RA. Only one patient was rheumatoid factor (RF) positive and none were anti-cyclic citrullinated peptide (CCP) antibody positive.[2] Jorgensen *et al*. reported nine patients with monoclonal gammopathy and MAA. All of the patients were seronegative for RF, and the majority had the hand and wrist involvement, including two patients who had

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Table 1: Hematological and biochemical profile of the two cases

Parameter (unit)	Normal range	Case 1	Case 2
Hemoglobin (g/dL)	13.5-17.5	9.6	8.2
Total leukocyte count ($\times 10^9$/l)	4.5-11.0	6.7	7.5
Platelets ($\times 10^9$/l)	150-350	167	203
Creatinine (mg/dL)	0.6-1.5	1.2	1.0
Total protein (g/dL)	6.0-8.3	7.3	8.1
Albumin (g/dL)	3.3-5.0	3.2	3.8
Calcium (mg/dL)	8.5-10.5	9.7	9.2
SPEP M-band (g/dL)	<3	2.3	1.2
Serum immunofixation	Negative	Lambda light chain	Lambda light chain
Serum free light chain (mg/L) (Kappa/Lambda)	Negative	Lambda=12,345 (0.009)	Lambda=3547 (0.02)
Troponin T (ng/ml)	0.00-0.09	<0.01	0.02
Bone marrow examination (%)	<10 clonal plasma cells	20	15

SPEP=Serum protein electrophoresis

distal interphalangeal joint involvement.[8] Vitali *et al*. published a similar series of four cases in which two patients who were RF negative, had rheumatoid-like, symmetric polyarthritis of the MCP joints and wrists.[9] Srinivasulu *et al*. published a case series of 6 patients, 5 of which were seronegative for RF and anti-CCP antibodies and 1 was positive for both.[10]

Most of these patients respond to bortezomib-based therapy. In the case report published by Patil and Oak, both patients who were diagnosed with amyloid arthropathy responded well to bortezomib and dexamethasone chemotherapy regimen.[11] In the case series by Srinivasulu *et al*., 3 of the 6 patients were treated with the bortezomib-based regimen.[10] Similarly, many other cases

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have been reported in the literature where either thalidomide or bortezomib-based chemotherapy has been given.[2,7]

Our first case with clinical features resembling RA, she had bilateral symmetrical swelling with tenderness in multiple joints of extremities, including MCP and PIP joints. Her RF and anti-CCP were negative, and she was treated as seronegative RA with methotrexate therapy. Following the worsening of symptoms and re-evaluation, a diagnosis of multiple myeloma with MAA was made. The second patient had symmetrical polyarthritis. Laboratory evaluation for RA was negative, and a provisional diagnosis of fibrosing tenosynovitis was made. Hematological investigations were suggestive of multiple myeloma. Synovial biopsy from the MCP joint was suggestive of amyloid deposits. Both patients had lambda light chain myeloma and responded well to bortezomib-based chemotherapy. In our patients, amyloid deposition was seen around the joints, as confirmed by synovial biopsy.

In conclusion, it is necessary to consider MAA in the differential diagnosis of patients presenting with clinical symptoms similar to that of RA or other seronegative spondyloarthropathies so that this syndrome can be made promptly diagnosed and appropriate therapy can be instituted early.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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