Case Report

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Multiple myeloma characterized by synovial fibrinoid necrosis: a case report

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Abstract

A number of patients with multiple myeloma (MM) have joint lesions with the main feature of amyloidosis or tumor cell infiltration. We report a case of MM that presented as synovial fibrinoid necrosis. The rarity of this condition and the difficulty diagnosing the disease are discussed. In addition, we discussed the characteristics of amyloid arthropathy and the findings in this case.

Keywords

Multiple myeloma, synovial fibrinoid necrosis, joint pain, amyloid arthropathy, synovial biopsy, amyloidosis

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Introduction

MM is a malignant proliferative disease of plasma cells. Abnormal proliferation of clonal plasma cells in bone marrow and the secretion of monoclonal immunoglobulin or its fragment M protein lead to related organ or tissue damage. Common complications of MM are bone destruction, hypercalcemia, hyperviscosity syndrome, hematological complications (e.g., anemia, thrombosis), kidney damage, amyloidosis, and infection. Myeloma bone disease is a common complication of MM that is characterized by osteolysis and osteopenia caused by increased osteoclast activity. Myeloma bone disease is also accompanied by osteoblast inhibition.[1] Therefore, the clinical

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manifestations are osteoporosis and pathologic fracture. Lesions affecting patients' joints in MM are amyloidosis and tumor cell infiltration. Amyloid formation in the synovial membranes may lead to an uncommon form of arthritis that is generally referred to as amyloid arthropathy. Numerous cases of MM-associated amyloid arthropathy (MAA) have been reported in the literature.[2] In addition, the results of numerous synovial biopsies from patients with MAA have been reported in the literature.[2] To date, no cases of synovial fibrinoid necrosis as the main feature have been reported. We report a case of MM with the primary feature of synovial fibrinoid necrosis.

Case report

A 55-year-old male patient was admitted to our hospital with pain in multiple joints. He complained of general joint pain, limb numbness, and weakness for 1 year and standing difficulty for 20 days. At first, these symptoms were alleviated with rest. However, pain gradually increased and was focused in his neck, shoulders, and hips. Ten months before presenting to our hematology department, he underwent right hip arthroplasty following a fracture of the right femoral neck because of osteoporosis, and he recovered well after the operation. Nine months before presenting to our hematology department, his hip pain worsened, but no significant cause was found. Five months later, he developed bilateral shoulder pain, and 10 days later, he underwent left hip and bilateral shoulder mass biopsies and resection. Four months later, he underwent right shoulder lesion exploration and resection, and 6 months later, he underwent left hip and left shoulder lesion exploration and resection. Pathological examination revealed fibrinoid necrosis of the synovium of the left hip and both shoulders. Fibrinoid necrosis was predominant in the left hip. We also identified focal fibrosis with chronic inflammatory cell infiltration and stromal angiomatous hyperplasia (Figure 1). Ten days after the left hip and shoulder surgeries, he was admitted for spine surgery. He underwent bone marrow aspiration to identify the cause of low hemoglobin, and the results indicated MM. He was then transferred to the department of hematology. Over the

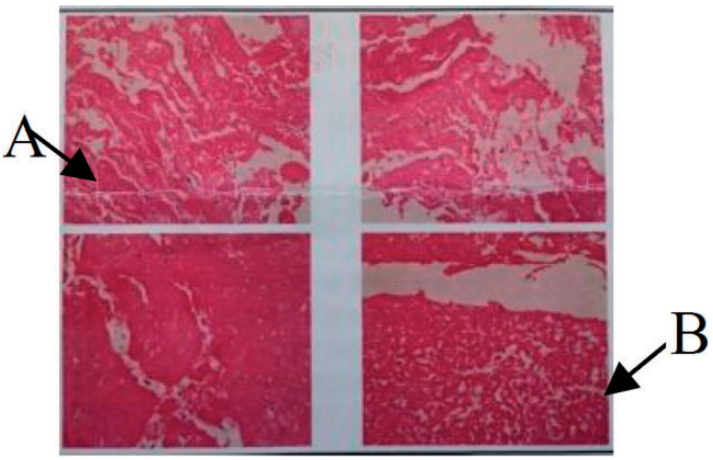

Figure 1. Pathological examination.
a: linear fibrinoid necrosis; b: granular fibrinoid necrosis.

next 20 days, he developed adduction of both upper limbs, flexion in the lower limbs, and involuntary twitching of the lower limbs when standing. He was eventually unable to sit up and walk independently. As a result of bilateral lower limb swelling, and joint stiffness and pain, it was difficult to maintain a normal position. He could lie down with both lower limbs flexed, for 3 minutes, and maintain the sitting position with his lower limbs hanging by the bedside, for 3 minutes. His position was adjusted every 3 minutes with the help of relatives, after which he was able to sleep for 3 minutes. From the illness onset, he had an abnormal appetite, defecation problems, and poor sleep. His weight was not evaluated because he could not stand, and he felt he had lost weight over these 20 days.

Medical history

The patient had a history of smoking and alcohol use but was not addicted. He had no special family history.

Physical examination

On physical examination, the patient's vital signs were stable; his heart rate was 112 beats per minute. He was alert, in poor spirits, emaciated, and in acute distress, with a passive posture. His palpebral conjunctiva was pale, but the sclera was not icteric. No obvious abnormalities were seen on cardiopulmonary and abdominal examinations. Limb movement disorder was evident; both upper limbs were in adduction, and both lower limbs were flexed at 90 degrees. Moreover, his knees, shoulders, and hips were stiff, and he was unable to move autonomously or passively. His wrist joints (Figure 2a), scapula (Figure 2b), and lower back (Figure 2c, 2d) had prominent masses that were hard, but not tender or mobile. His knees, elbows, ankles, and fingers were swollen, and his cervical physiological curvature had straightened, cervical tenderness was present, and cervical movement was limited. Facial and neck sensation were normal, but hypoesthesia was present in the skin of his limbs. His bilateral upper limb muscle strength was grade I, and bilateral lower limb muscle strength was grade II. His muscle tone was high, and neither bilateral knee tendon reflexes nor the Achilles tendon reflex were elicitable; bilateral Babinski signs were inconclusive.

Investigations

Laboratory testing revealed the following: white blood cell count: 9.9×10^9/L (range, 3.5–9.5); neutrophils: 6.49×10^9/L (range, 1.8–6.3); red blood cells 2.79×10^{12}/L (range, 4.3–5.8); hemoglobin: 79 g/L (range, 130–175); platelets: 363×10^9/L (range, 125–350). Urine protein was positive in the urinalysis, and the fecal occult blood test result was positive. Blood β2 microglobulin concentration was 1087.36 nmol/L (range, 67.85–237.49), and

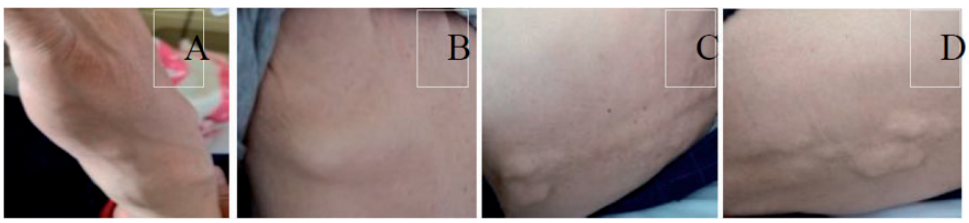

Figure 2. Joint masses.
(a) wrist joints; (b) scapula; (c, d) lower back.

serum ferritin was 520 μg/L (range, 15 000–200 000). Liver function testing revealed the following: total protein: 55.8 g/L (range, 65–85) and albumin: 29.7 g/L (range, 40–55). Renal function testing revealed the following: creatinine: 137.6 μmol/L (range, 55–104), glucose: 9.41 mmol/L (range, 3.8–6.15), and urea: 13.90 mmol/L (range, 1.8–8.3). Immunoglobulin G (IgG) concentration was 3.28 g/L (range, 8–18), IgA: 0.256 g/L (range, 0.9–4.5), and IgM: 0.169 mg/dL (range, 0.7–2.8). The erythrocyte sedimentation rate was 39.0 mm/h (range, 0–15), and the myocardial zymogram results revealed: aspartate aminotransferase: 0.68 μkat/L (range, 0–0.67), lactate dehydrogenase: 4.44 μkat/L (range, 0.67–3.67), creatine kinase-MB 48.2 U/L (range, 0–16), and hydroxybutyrate dehydrogenase: 206 U/L (range, 90–200). Blood coagulation testing revealed the following: antithrombin III: 313 mg/L (range, 170–300), fibrin degradation products: 5.77 mg/L (range, 0–5), and D-dimer: 10.35 nmol/L (range, 0–3.01). The pro-brain natriuretic peptide concentration was 6400 ng/L (range, 0–100); interleukin-6 (IL-6) concentration: 7.62 pg/mL (range, 0–5.4); C-reactive protein concentration: 35.82 mg/L (range, 0–5); serum protein electrophoresis revealed kappa type M proteinemia. Serum free light chain κ concentration was >4125 mg/L (range, 3.30–19.40); free light chain λ: 12.5 mg/L (range, 5.71–26.3); the κ/λ ratio was >330 (range, 0.26–1.65). Antinuclear antibody (ANA), rheumatoid factor, anti-streptolysin O, 25-hydroxyvitamin D3, thyroid function, blood-borne diseases, Bence–Jones proteins, and electrolyte concentrations were within normal limits. Bone marrow aspiration revealed abnormal plasma cells, which accounted for 45.5% of all cells, indicating multiple myeloma (Figure 3).

Lower limb venous ultrasound revealed thrombosis in the proximal left deep femoral vein and in the superficial femoral vein.

Abdominal and renal tract ultrasonography revealed renal cysts.

Spine X-rays revealed instability in cervical (C)2–C3 vertebrae, and an asymmetrical atlanto-ulnar space measuring approximately 6 mm wide. The cervical curvature was abnormal, and hyperostosis was evident in the C2–3, C3–4, C4–5, and C5–6 vertebral spaces. Bony destruction was evident in bilateral humeri, collarbones, scapulae, cervical vertebrae, appendages, multiple ribs, pelvis, and both femurs. There was subluxation in the right shoulder, and decreased bone density and hyperosteogeny in both knees, with effusion in the suprapatellar bursa and articular spaces of both knees.

At the slope of the cervical vertebrae in axial CT images, the occipital region and shoulder joint bones had uneven density.

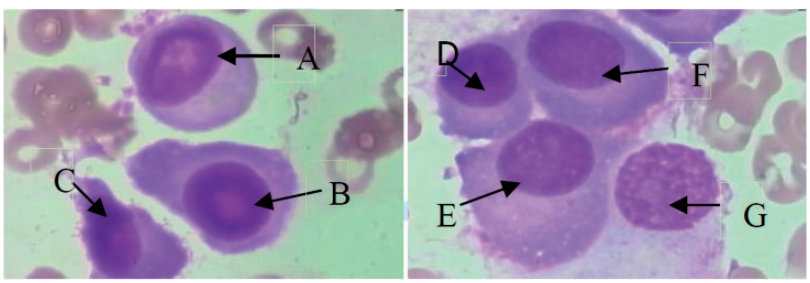

Figure 3. Bone marrow morphology.
a, b, d: plasmablasts; c, e, f: immature plasma cells; g: senescent plasma cell.

Bony destruction and soft tissue masses in the paravertebral, caudal cervical region, bilateral shoulder joints, and subclavian region were detected. There were many nodular low-density foci in bilateral scapulae. The right vertebral artery appeared normal in the intracranial and atlas segments, and the left vertebral artery was narrowed in the transverse view. Bronchitis and local emphysema were visible in the right upper lung lobe. The right middle lung lobe, the lingual segment of the left lung, and the margins of the lower lobe in both lungs contained irregular linear opacities. There was bilateral pleural thickening, local adhesions, a small amount of pericardial effusion, and widening of the trunk of the pulmonary aorta.

Magnetic resonance imaging revealed abnormal bone changes in the cervical, thoracic, and lumbar vertebrae and in the small joints. C2–6 intervertebral disc herniation and lumbar 4–sacral 1 intervertebral disc herniation were also detected.

Admission diagnoses: 1. KAP multiple myeloma (DS stage III and ISS stage III); 2. previous left femoral vein thrombosis; 3. bronchitis and emphysema; 4. hypoproteinemia; 5. pericardial effusion; 6. C2 spinal stenosis; 7. vertebral disc bulging between the C3–T1 vertebrae and vertebral disc bulging between the L4–S1 vertebrae; and 8. cervical degenerative disease. From March 8, 2020, our treatment plan involved bortezomib (1.9 mg on days 1, 4, 8, and 11) and dexamethasone (20 mg on days 1–4 and days 9–12). Concurrent hydration therapy, alkalinization, and liver and stomach protection were also provided. During the treatment, the patient's condition remained stable, and no obvious adverse reactions were observed. Seventeen days after the first course of treatment, the patient returned to the hospital for the second course of treatment. At this time, he was lucid and in good spirits, with normal facial expression. His posture and sleep had improved significantly, and he could maintain both the sleeping and sitting positions for 30 minutes at a time. He was now also able to sleep for 30 minutes at a time. He felt he was gaining weight, and his systemic bone pain was relieved. Passive movement was possible in both upper limbs, and he could perform a small degree of voluntary movement. The flexion in both lower limbs improved significantly to 160 degrees. The physiological curvature in his cervical spine gradually recovered, and mobility in his cervical spine increased obviously. Even more delightful, superficial sensation in his limbs recovered, and the knee tendon reflex was $++$. His white blood cell count was 5.77×10^9/L (range, 3.5–9.5), red blood cell count: 2.54×10^{12}/L (range, 4.3–5.8), hemoglobin: 73 g/L (range, 130–175), platelet count: 304.00×10^9/L (range, 125–350), C-reactive protein: 20.24 mg/L (range, 0–5), creatinine: 75.00 μmol/L (range, 55–104), urea: 8.90 mmol/L (range, 1.8–8.3), blood β2 microglobulin: 7.920 mg/L (range, 0.8–2.8), and pro-brain natriuretic peptide: 79.92 ng/L (range, 0–100). Bone marrow aspiration revealed that the percentage of plasma cells was 11.5%.

Discussion

Joint lesions in patients with MM are characterized by bone pain and amyloidosis. Bone pain is present in 58% of MM patients, and pain tends to be moderate to severe, with post-exercise aggravation.[3] The typical sites of pain are the chest and back, and the incidence of limb pain is approximately 1%.[4] Only 0.1% to 6% of MM patients have amyloidosis.[5] Light chain (AL) aggregation in characteristic beta pleated sheets results in the formation of amyloid, termed AL amyloid.[6] AL amyloidosis is more common in patients with amyloid arthropathy. Monoclonal gammopathies, such as MM or Waldenstrom's macroglobulinemia can lead to AL amyloid

formation. Amyloid arthropathy can be divided into two types. If amyloid is deposited around the joint tissues and synovia, the affected joint develops edema and swelling, which can lead to a misdiagnosis of rheumatoid arthritis. When bone marrow is replaced with amyloid, larger joints (e.g., the hip joint) are often affected, and fractures can occur frequently.[7] Amyloidosis may be found in muscle and bone tissue by pathological examination. The usual hallmarks of chronic inflammatory synovitis (inflammatory infiltration, intimal hyperplasia, and stromal proliferation[8]) were reported relatively rarely, and increased vascularity was reported in only 2/15 (16.7%) cases.[2] Our patient's synovial biopsy revealed both the usual hallmarks of chronic inflammatory synovitis and increased vascularity. In the absence of humoral immunity, amyloid phagocytosis by synovial-specific phagocytes is a key element in the pathogenesis of MAA. In relatively mild synovitis, the majority of the mononuclear inflammatory cells were identified as cluster of differentiation (CD) 68 þ macrophages.[9] This finding is not consistent with the results of our patient's synovial biopsy; thus, we infer that there are still important and unknown factors in the pathogenesis of MAA. Compared with general MAA patients, our patient had more severe symptoms and lower concentrations of IL-6. Usually, patients with advanced MM are considered to have a poor prognosis; however, the effect of bortezomib in our patient was excellent. MM characterized by synovial fibrinoid necrosis appears to be a type with severe symptoms but a better prognosis. We speculate that fibrinoid necrosis may cause more damage to patients' bones. In our literature review, we found no reports of MM with multiple synovial fibrinoid necrosis as the initial feature, as in our case. Fibrinoid necrosis is a type of necrosis of the interstitial collagen fibers and small vessel walls. The tissue structure of the lesion gradually disappears and transforms to granular, small, or lumpy nonstructural material, which is strongly eosinophilic, as for fibrin. However, the nature and formation mechanism of fibrinoid substances are unknown. Fibrinoid necrosis is common in autoimmune diseases, such as acute rheumatism, systemic lupus erythematosus, and glomerulonephritis. The combination of our patient's medical history and investigation findings excluded the above-mentioned autoimmune diseases. With the improvement in our patient's symptoms and test results after treatment with bortezomib, we consider that the synovial fibrinoid necrosis was caused by MM. All of the pathological findings were obtained from the patient's biopsy during the surgery. Because the patient refused synovial biopsy while he was undergoing treatment in the department of hematology, we were unable to obtain additional pathological findings and study the causes of synovial fibrinoid necrosis in MM. Owing to the unique pathological findings in the synovial biopsy, the patient was misdiagnosed with a pathological fracture after several joint operations. It is regrettable that the patient was not properly diagnosed and treated within 10 months because this caused additional suffering and financial burden. Reporting the clinical features of this case has an important role in improving clinicians' understanding of similar patients, and in reducing misdiagnosis and incorrect treatment.

Ethics statement

This study was approved by the Ethics Review Committee of the Affiliated Hospital of Yan'an University. The patient is aware of the contents of this report and provided consent for publication.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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