Waxy Nodules: As a Cutaneous Diagnostic Mirror of Systemic Disease Mimicking Rheumatoid Arthritis

Dear Editor,

In practice, rheumatoid arthritis (RA) is a common diagnosis made when a middle-aged adult presents with bilateral symmetrical polyarthritis, even in the absence of rheumatoid factor and/or anticyclic citrullinated peptide antibodies. Primary systemic amyloidosis is a rare type of systemic amyloidosis, due to protein AL amyloid involving internal organs, peripheral nerve tissue, and skin usually idiopathic or associated with multiple myeloma. We report a case of primary systemic amyloidosis with chronic polyarthralgia which was diagnosed and treated as rheumatoid arthritis earlier.

A 54-year-old female was referred by the medical department for asymptomatic skin lesions present on her lips, hands, and both eyelids noticed since one year. Initially, she noticed raised small skin-colored lesions over eyelids along with an increase in size of tongue and gradually progressed with an increase in size and number of similar lesions over hands, neck, groin, and lips within a year. She was apparently normal four years back, when she developed pain in her right wrist followed by left wrist. She was diagnosed with carpel tunnel syndrome and surgical release was done. She had insidious onset, moderately severe nonradiating pain of both shoulder joints, knee joints, and small joints of hands and was diagnosed with rheumatoid arthritis and started on systemic steroids, methotrexate, chloroquine, and colchicine since March, 2022 from another hospital. She was a diagnosed case of hypothyroidism and hyperuricemia on treatment since four years. There is no significant family history and is normotensive and nondiabetic.

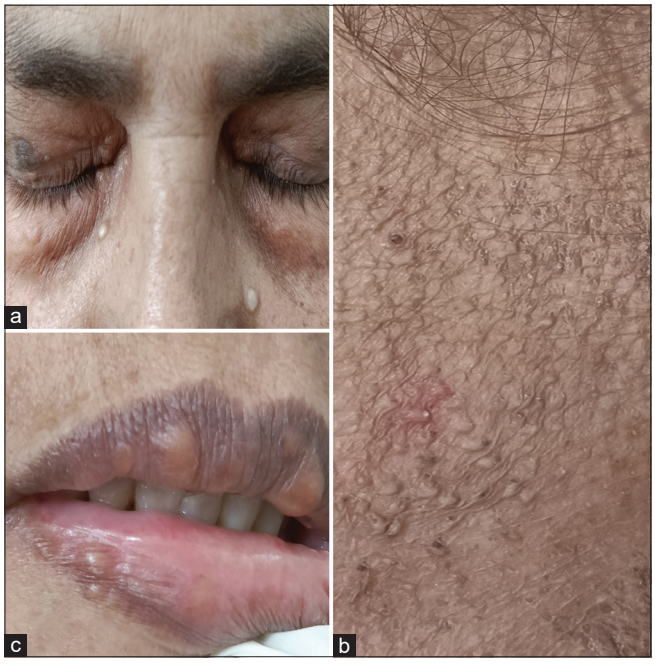

Figure 1: (a) Few papules, milia-like, a few coalescing to form band-like lesions over bilateral eyelids (b) Multiple skin coloured and firm papules grouped over neck along with purpura (c) Multiple shiny, smooth, firm, waxy coloured spherical nodules over both upper lips, lower lips, and vermillion border

On dermatological examination, multiple shiny, smooth, firm, waxy colored spherical papules and nodules, a few coalescing to form band-like lesions, and multiple milia-like lesions over bilateral eyelids, upper and lower lips including vermillion border, and buccal mucosa were present. Lesions over neck and bilateral crural folds resembled pseudoxanthoma elasticum [Figure 1]. The tongue was greatly enlarged, with a white coating and the lateral aspect showed indentations from the teeth [Figure 2]. Multiple purpuric and ecchymotic lesions were present on neck and bilateral upper limbs. Both hands showed scleroderma-like skin changes with firm, skin-colored nodules and postsurgical scar [Figure 3]. Other mucosae, hair, and nails appeared normal. Musculoskeletal examination showed enlarged bilateral anterior shoulders (shoulder pad sign positive), wasting of thenar and hypothenar muscles, partially restricted and painful joint movements, and no tenderness or contractures with a normal gait. No other relevant systemic examination findings were seen. A provisional diagnosis of systemic amyloidosis, primary or secondary, was made based on previous history of carpal tunnel syndrome, clinical features of nodular skin lesions, purpura, macroglossia, and rheumatoid-arthritis like arthropathy. Other differential diagnoses include rheumatoid nodules, sarcoidosis, lipoid proteinosis, and mucinosis. Clinically, rheumatoid

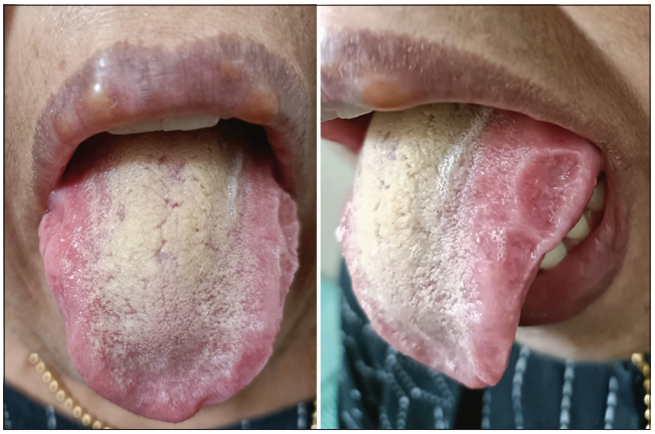

Figure 2: Macroglossia with a white coating and the lateral aspect showed indentations from the teeth

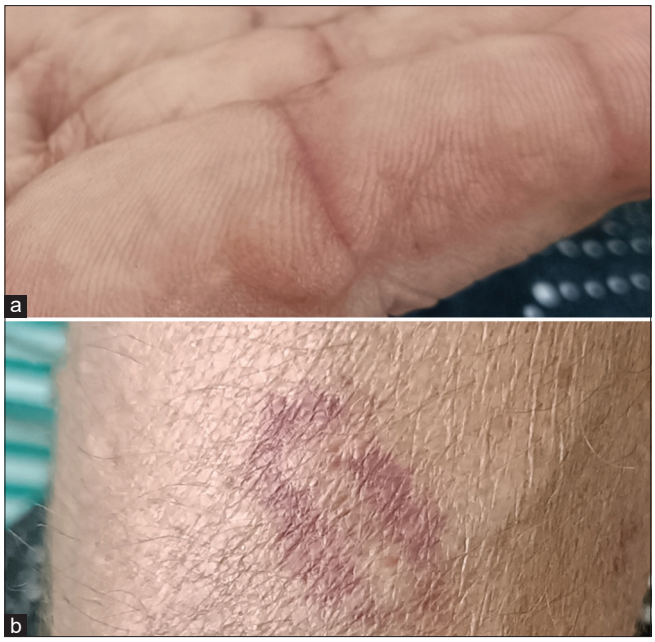

Figure 3: (a) Right index finger showed scleroderma like skin changes with firm, skin-colored nodules of scleroderma amyloidosum gottron (b) amyloid purpura over right forearm

nodules present as nonwaxy, firm, skin-colored nodules on extensor surfaces and areas of pressure or repetitive trauma frequently attached to periarticular capsule.

Routine laboratory tests showed mild anemia (hemoglobin: 10.5 g/dL), neutrophilic leukocytosis (Total Count: 13,500/cumm, neutrophil: 85%, lymphocyte: 13%, eosinophil: 2%), raised erythrocyte sedimentation rate (ESR) (60 mm/hr), C-reactive protein (CRP) (7.92 mg/L), lactate dehydrogenase (LDH) (295 IU/L), altered renal function test (blood urea: 65 mg/dL, serum creatinine: 1.3 mg/dL, serum uric acid: 7 mg/dL), 24-hour urine protein level of 134 mg/day, and normal levels of liver function test including albumin globulin ratio, serum angiotensin converting enzyme (ACE) levels, serum electrolytes, and thyroid hormone levels. Autoantibodies including rheumatoid factor, anticyclic citrullinated peptide, antinuclear antibody, and antineutrophil cytoplasmic antibodies were all negative. Serum protein electrophoresis showed a monoclonal pattern of M-spike at gamma fraction (concentration: 0.53 g/dL) and mildly decreased albumin fraction (concentration: 3.37 g/dL). Abdominal ultrasound showed generalized lipomatosis in subcutaneous fat, diffuse intraabdominal, retroperitoneal, pelvic, pancreatic and renal fat, hepatomegaly with grade 1 fatty changes, and renal parenchymal changes. The chest radiograph, electrocardiogram, echocardiography, cardiac stress test, cardiac troponin T levels, and skeletal radiographs of skull and joints of upper and lower extremities showed no abnormalities, except for soft-tissue prominence overlying deltoid muscle. Histopathological examination of skin nodules from right hand and upper lip showed hyperkeratotic epidermis, superficial, and

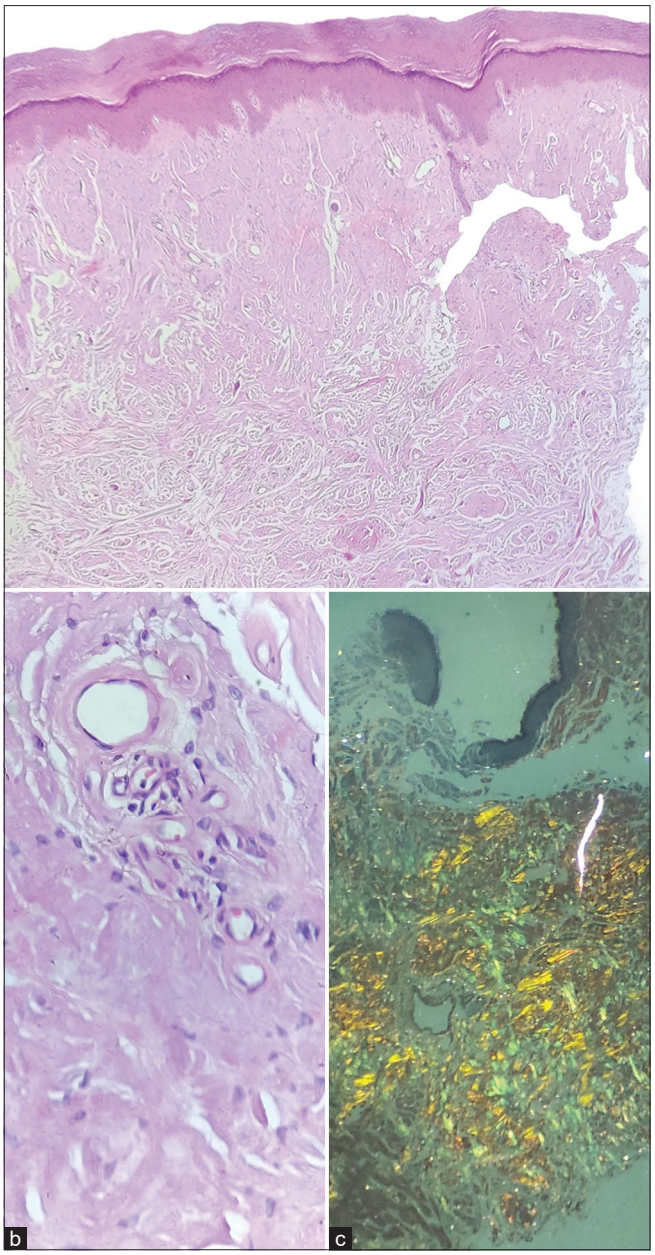

Figure 4: (a) Hyperkeratotic epidermis, superficial, and deep dermis showed aggregates of amorphous fissured eosinophilic material (H&E 4x) (b) Amyloid deposits in dermis including perivascular infiltrate (H&E 4x) (c) Apple green birefringence under polarized light

deep dermis showed aggregates of amorphous fissured eosinophilic material [Figure 4a and 4b]. Congo red staining showed apple green birefringence [Figure 4c] under polarized light confirming the diagnosis of primary systemic amyloidosis. She was referred for evaluation of monoclonal gammopathy, bone marrow aspirate showed cellular marrow with trilineage hematopoiesis with 4% of plasma cells, bone marrow trephine biopsy showed cellular marrow with trilineage hematopoiesis with no significant increase in plasma cells, and CD138 immunohistochemistry showed 8% positivity of cells. The immunoglobulin free light chain assay showed raised lambda-free light chain level (27.8 mg/L) with normal kappa-lambda ratio.

Primary systemic amyloidosis is the most common and severe form of systemic amyloidosis in the developed countries. It occurs more in males and the average age at presentation is 64 years. It affects 8-12 per million patients per year.[1] The most common causes are monoclonal gammopathies, accounting for about 70% of cases, followed by multiple myeloma (20%), and Waldenström's macroglobulinemia (10%).[2]

Diagnosis of this disguised disease unfurled the importance of arthropathy, hypothyroidism, and hyperuricemia in our patient. Amyloid arthropathy occurs chiefly as a manifestation of β2 microglobulin amyloidosis in patients receiving chronic hemodialysis and in 3.5% of amyloidosis-complicated multiple myeloma. Although clinically amyloid arthropathy can be confused with RA, radiologically, it shows bone cysts, but preservation or even widening of the joint spaces are the distinguishing features. The "shoulder-pad" sign resulting from periarticular soft-tissue amyloid deposition is pathognomonic for immunoglobulin AL amyloidosis.[3] Amyloid infiltration of the muscles causes pseudohypertrophy, chronic pain, and weakness, which usually occurs in the shoulder girdle giving an impression of well-developed shoulder musculature, termed the 'shoulder-pad' sign.

As per a study by Muchtar *et al*., about one-fifth of patients with AL amyloidosis had elevated serum TSH value with overt or subclinical hypothyroidism. AL amyloidosis is a major driver for the thyroid dysfunction and mimics hypothyroidism symptoms.[4]

Elevated serum uric acid levels have been associated with cardiovascular mortality in AL amyloidosis and forecast probable outcomes in patients with chronic heart failure. The median survival from diagnosis of AL is 3 years; chronic heart failure predicts survival of less than 1 year.[5] Fortunately, in our case, the diagnosis was made before the development of cardiomyopathy, a complication significantly reducing life expectation.

This case report highlights the diversity of presentation of AL amyloidosis and stresses the importance of arthropathy as a potentially under-recognized presenting manifestation of monoclonal gammopathies. As it can be a diagnostic primer of underlying diseases including multiple myeloma, detailed history and laboratory investigation must be implemented on suspicion of amyloidosis because early recognition of amyloid-associated diseases and appropriate treatment can improve clinical outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/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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