Nodular amyloidosis of the lips as a presenting feature of systemic amyloidosis associated with multiple myeloma

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INTRODUCTION

Multiple myeloma (MM) is an uncommon malignancy that involves proliferation of atypical plasma cells in the bone marrow, generally diagnosed in the seventh decade of life.[1] Initial clinical signs and symptoms associated with MM are variable but usually include bone pain, anemia, hypercalcemia, and renal insufficiency. It is estimated that approximately 10% to 15% of patients with MM have concomitant immunoglobulin amyloid light-chain (AL) amyloidosis[2,3]; of those patients, 29% to 40% have mucocutaneous disease.[4] Here, we report a case of isolated nodules on the bilateral oral commissures as an unusual presenting sign of systemic AL amyloidosis, uncovering a diagnosis of MM.

Abbreviations used:

AL: amyloid light chain
MM: multiple myeloma

CASE REPORT

A 71-year-old man with past medical history relevant for carpel tunnel syndrome presented with 2 painless nodules on the corners of his lower lip that had been developing for several years. He noted that the lesions had become increasingly bothersome and had a tendency to bleed after shaving or picking at the area. His review of systems was otherwise significant only for sinus congestion.

Physical examination showed 2 well-defined, firm, yellow-to-red nodules with overlying telangiectasias on bilateral lower mucosal lips (Fig 1) that bled when nicked. No other mucocutaneous findings were noted. Clinical diagnoses high on our differential included nodular solar elastosis and enlarged Fordyce spots.

Pathologic study results of both nodules indicated severe solar elastosis displaced by nodular aggregates of pale, homogenous eosinophilic deposits in the papillary and upper reticular dermis that stained with Congo red under polarized light (Fig 2). Gray solar elastotic fibers were sparsely present within the eosinophilic deposits, highlighted by Verhoeff's Elastic Stain. Plasma cells were not prominent. Liquid chromatography and tandem mass spectrometry detected a peptide profile consistent with AL kappa-type amyloid deposition. These findings supported the diagnosis of nodular cutaneous amyloidosis, and further workup was initiated to evaluate for systemic disease.

Blood count, basic chemistry panel, and liver function panel results were unremarkable, except for a mildly decreased total protein level of 5.7 g/dL (normal range, 6-9 g/dL). Serum and urine electrophoresis and immunofixation showed the presence of abnormal monoclonal kappa light chains and a faint band of lambda light chain. Serum-free light chain assessment uncovered a kappa-to-lambda ratio of 122:81 (normal, 2:1).

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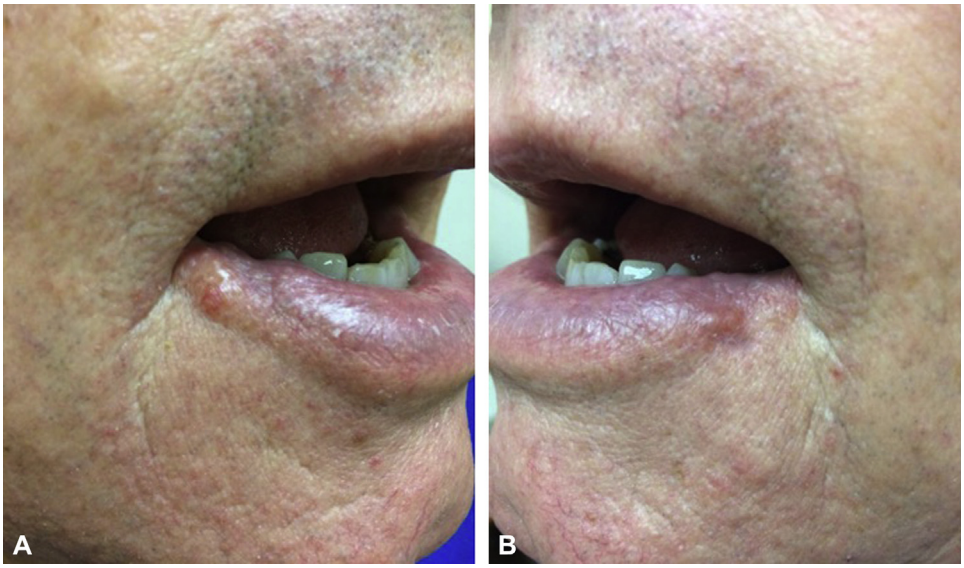

Fig 1. Well-defined, firm, yellow-to-red nodules with overlying telangiectasias on the lower part of the **(A)** right and **(B)** left lip.

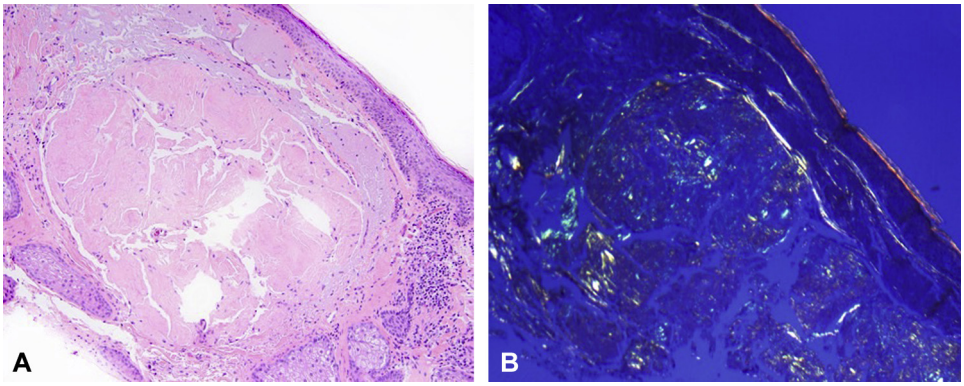

Fig 2. Homogenous eosinophilic deposits in the papillary dermis **(A)** under hematoxylin-eosin staining and **(B)** staining positive with Congo red for apple green birefringence under polarized light.

A bone marrow biopsy specimen showed hypercellular bone barrow (50% cellularity) with diffuse involvement by $CD138^{+}$ plasma cells (50% involvement) and mild focal increase in reticulin fibrosis; no excess blasts were noted. On flow cytometric analysis, population of cytoplasmic kappa-restricted plasma cells was noted. Given the results of this comprehensive workup, diagnosis of multiple myeloma was made. Imaging displayed no evidence of lytic lesions in the bone; however, amyloid deposits were found throughout various organ systems, including the skin, oral mucosa, and gastrointestinal tract. The patient was referred to hematology/oncology specialists for further management. Given the extent of disease, this patient was enrolled in a clinical trial to reverse the progression of MM.

DISCUSSION

AL amyloidosis represents a spectrum of disease that is characterized by extracellular deposition of insoluble fibrils of monoclonal light chains. Organs most commonly affected include kidney, heart, liver, nerves, and gastrointestinal tract, but any organ or tissue can be affected, including the skin. The condition, alone or in conjunction with underlying plasma cell dyscrasias, including MM, is commonly diagnosed when patients are in their 60s[5]

Skin findings secondary to myeloma-associated AL amyloidosis are variable in presentation, with bullae (56%) being the most commonly reported lesion, followed by purpura/ecchymoses (25%) and nodules/papules (16%); a few cases of scleroderma, macroglossia, alopecia, nail dystrophy, and

condyloma have also been reported.[5] Nodular and papular lesions, seen in our patient, are caused by direct dermal infiltration of amyloid; they classically appear yellow, shiny, smooth, waxy, and often hemorrhagic and are found on flexor surfaces, face, neck, or buccal mucosa.[4] Amyloid also has the propensity to infiltrate cutaneous blood vessels, potentially causing friability and bleeding,[6] as seen with manipulation of our patient's lesions. Skin and mucosal involvement in MM-associated AL amyloidosis is not uncommon; however, the papular/nodular variant is rare and, in this case, was the only readily apparent manifestation of disease.

It is critical to recognize early manifestations of AL amyloidosis because 30% of patients at the time of diagnosis already have involvement of more than 3 organs.[7] Furthermore, early diagnosis reduces the rare possibility of progression of AL amyloidosis to overt MM.[8] Although there has been progress made in the treatment of patients with MM, management approaches for AL amyloidosis associated with MM are generally not well defined. Prognosis for patients of myeloma-associated AL amyloidosis is poor, with reported median survival as short as 4 months to 5 years.[5] Prognosis of patients with skin involvement is even worse, potentially reflecting extensive systemic involvement.[5]

Although screening for cutaneous neoplasms is well within the lexicon of dermatology, identifying systemic malignancies is also an important role for dermatologists, who continue to evaluate a modest proportion of patients with gammopathy.[9] Dermatologists are in a unique position for early diagnosis of this disease, especially for patients with mucocutaneous findings without overt evidence of systemic symptoms or organ dysfunction. In our patient, pathologic evaluation of resected specimens produced an incidental finding that served as a key diagnostic test, allowing for diagnosis before the development of more severe signs and symptoms. This case highlights the benefits of dermatologic evaluation in conjunction with judicious pathologic screening as an important gateway for diagnosis in those who are at high risk for such gammopathies, such as AL amyloidosis and MM. These conditions should remain part of the differential diagnosis for chronic cutaneous lesions in such patients.

CONCLUSION

In summary, we present a case of systemic AL amyloidosis associated with MM with a sole initial presentation of nodular cutaneous amyloidosis on the corners of the lips. This exemplifies the importance of meticulous mucocutaneous surveillance and judicious pathologic testing, which may provide contextual clues for accurate diagnosis. This may lead to an earlier diagnosis, more timely treatment, and improved patient outcomes.

REFERENCES

1. National Cancer Institute. Myeloma fact sheet. Surveillance Epidemiology and End Results Program. Available at: https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed June 12, 2019.
2. Oshima K, Kanda Y, Nannya Y, et al. Clinical and pathologic findings in 52 consecutively autopsied cases with multiple myeloma. *Am J Hematol*. 2001;67:1-5.
3. Ivanyi B. Frequency of light chain deposition nephropathy relative to renal amyloidosis and Bence Jones cast nephropathy in a necropsy study of patients with myeloma. *Arch Pathol Lab Med*. 1990;114:986-987.
4. Breathnach SM. Amyloid and amyloidosis. *J Am Acad Dermatol*. 1988;18:1-16.
5. Andrei M, Wang JC. Cutaneous light chain amyloidosis with multiple myeloma: a concise review. *Hematol Oncol Stem Cell Ther*. 2019;12(2):71-81.
6. Hamzavi I, Lui H. Excess tissue friability during CO_2 laser vaporization of nodular amyloidosis. *Dermatol Surg*. 1999;25:726-728.
7. Ventarola DJ, Schuster MW, Cohen JA, Silverstein DI. JAAD grand rounds quiz. Bullae and nodules on the legs of a 57-year-old woman. *J Am Acad Dermatol*. 2014;71:1035-1037.
8. Rajkumar SV, Gertz MA, Kyle RA. Primary systemic amyloidosis with delayed progression to multiple myeloma. *Cancer*. 1998;82:1501-1505.
9. Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light Chain Amyloidosis: patient experience survey from the Amyloidosis Research Consortium. *Adv Ther*. 2015;32:920-928.