Widely distributed purple-colored bullae and nodules in the oral cavity

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CLINICAL PRESENTATION

A 67-year-old man presented to the Department of Oral Medicine, West China Hospital of Stomatology (Sichuan, China), with complaints of hard, purple-colored masses present in the oral cavity for 5 months and painful ulcers present for 2 months. Five months earlier, he had noticed the appearance of purple-colored, hard masses in the tongue and bilateral buccal membrane, and these masses grew in number and volume. The volume of the tongue increased, and the tongue became inflexible, hampering eating and swallowing. Two months earlier, ulcers had appeared on the surface of the purple-colored masses, causing slight pain. In addition, the patient felt fatigued and had limited mobility of the right arm because of pain. His medical history included mild hypertension, but his blood pressure was under control with physical exercise and diet. He had no history of tuberculosis, rheumatism, or other systemic diseases; neither did he have any allergies or familial history of genetic diseases.

Intraoral examination revealed that the tongue was enlarged (Figure 1A) and somewhat inflexible. Widespread purple-colored, bulla-like masses or nodules of varying sizes were present in the tongue dorsum, lower labial mucosa, ventral tongue surface, and the buccal mucosa, bilaterally (Figures 1A−1F). The masses were firm on palpation. Moreover, three ulcerations were located in the middle of the lower labial mucosa, right ventral tongue surface, and left anterior tongue border, with an area of approximately 12 × 8 mm, 6 × 6 mm, and 4 × 4 mm, respectively (see Figures 1B−1D). Furthermore, ecchymoses were present around the purple-colored, bulla-like masses in the lower labial mucosa and bilateral buccal mucosa (see Figures 1B, 1E, and 1F). Extraoral examination showed ecchymoses and purpuras in the area of the right perioral skin (Figure 1G) and petechiae around the nipple (Figure 1H).

DIFFERENTIAL DIAGNOSES

We classified the patient's various oral and cutaneous lesions into 2 clinical types for the purpose of generating a differential diagnosis: the first clinical type comprised purple-colored, bulla-like nodules and macules suggestive of subcutaneous hemorrhage; the second clinical type included nodules with or without ulceration.

The first lesion type was considered a possible representation of a hematopoietic disorder, including primary idiopathic thrombocytopenic purpura (ITP) and leukemia.

Primary ITP is an acquired immune-mediated disorder characterized by a peripheral blood platelet count less than 100 × 109/L and the absence of any obvious initiating and/or underlying cause of the thrombocytopenia.[1] ITP signs in the oral cavity include petechiae, purpuras, ecchymoses, and spontaneous mucosal bleeding resulting in purple-colored blood bullae and hematomas.[2,3] Skin hemorrhage lesions are also common, and some patients present clear symptoms of fatigue.[4] However, the patient's platelet count was normal. Bleeding time and coagulation factors were also normal in this patient. Therefore, ITP was eliminated as a cause of the patient's symptoms.

Leukemias are hematologic malignancies that result from the clonal proliferation of hematopoietic stem cells. Complete blood counts in leukemias often show reduced erythrocyte and platelet counts, with notably elevated counts of white blood cells of either granulocytic or lymphocytic derivation. Oral manifestations include hemorrhagic macules, ulcerations, localized or diffuse gingival enlargement, and bleeding.[5] Petechiae, purpuras, and ecchymoses are usual presentations in the skin.[6] Patients may also have anemia, fatigue, and bone pain.[7] The oral and systemic manifestations of this patient were somewhat similar to those of leukemia. However, the routine blood test results in this patient were not consistent with leukemia. Although erythrocytes were reduced, the numbers of leukocytes and platelets were normal. Moreover, oral lesions were

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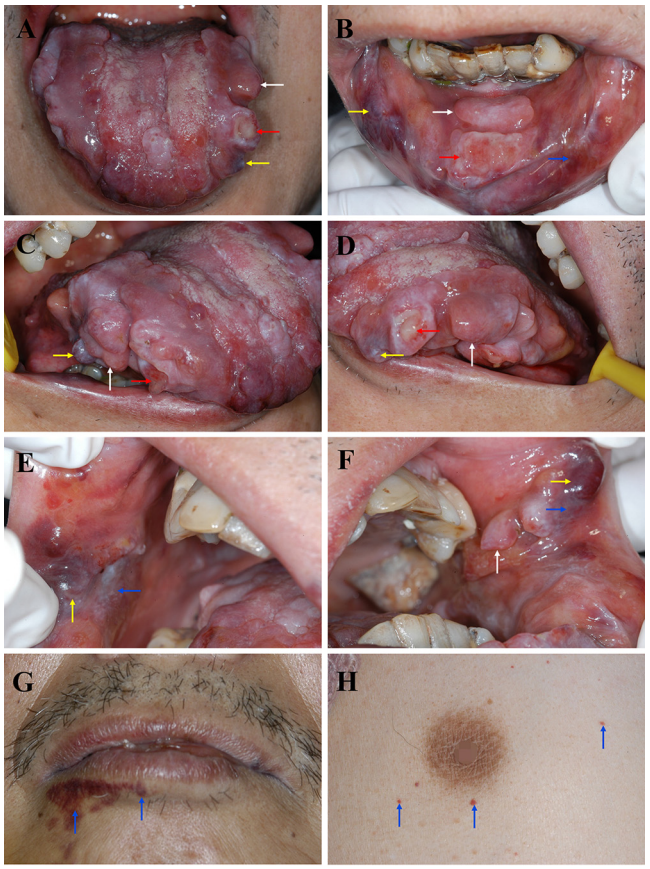

Fig. 1. Widespread oral and skin lesions. **(A–F)** Widely distributed purple-colored, bulla-like masses *(yellow arrows)* and nodules *(white arrows)* on the dorsal tongue, lower labial mucosa, ventral tongue, and the buccal mucosa, bilaterally. **(A–D)** Ulcerations on the tongue and lower labial mucosa *(red arrows)*. **(B, D–F)** Ecchymoses surround purple bullous masses in the lower labial mucosa and buccal mucosa *(blue arrows)*. **(G)** Ecchymoses and purpuric lesions in the right perioral skin *(blue arrows)*. **(H)** Petechiae adjacent to the nipple *(blue arrows)*.

widespread throughout the oral cavity, involving all areas, with the exception of the gingivae. In view of the composite laboratory and clinical findings, leukemia was ruled out.

The first type of lesion should also be distinguished from angina bullosa hemorrhagica (ABH). ABH is characterized by the acute formation of tense blood-filled blisters on slight trauma in the absence of blood dyscrasia, vesiculobullous disease, or systemic disease.[8] It mainly affects the soft palate in generally healthy adults. Other sites in the oral cavity, including the tongue, buccal mucosa, lip, and gingiva, may also be involved. The blisters can be solitary and large or generalized and small. Both types may be accompanied by pain. No treatment is required for ABH because spontaneous rupture and healing are expected within a short time frame. A large bulla should be incised to prevent further enlargement that could cause airway obstruction.[9] Although the hemorrhage lesions may have been exacerbated by trauma in our patient, the typical acute onset and the spontaneous healing of ABH was not consistent with the symptoms in our patient. In addition, nodules, ulcerations, and cutaneous hemorrhagic lesions are not present in ABH. Therefore, ABH was unlikely to be the diagnosis.

Oral Kaposi sarcoma (KS) was a consideration, given the abundance of nodular, ulcerated lesions. KS is attributable to human herpesvirus 8 infection, usually in the setting of HIV/AIDS.[10] On the oral mucosa KS lesions can be solitary or involve multiple sites. These include the hard and soft palates, the gingiva, and the dorsal tongue, presenting as macular patches, plaques, or nodular forms ranging in color from nonpigmented to brownish-red or violaceous. Exophytic KS lesions can be ulcerated, painful, and hemorrhagic.[11] The masses and ulcerations observed in our patient appeared clinically similar to the spectrum of findings seen in lesions of KS. However, in this patient, the HIV test result was negative.

On the basis of our consideration of the various possibilities that the clinical lesion types could represent, we concluded that what was most likely in this case was a systemic disorder, possibly neoplasia, with multicentric presentation. Therefore, representative biopsies were recommended.

DIAGNOSIS AND MANAGEMENT

The patient was referred to the Department of Oral Surgery. After providing written informed consent, the patient underwent incision biopsies of a purple-colored, bulla-like mass and a nodule in the tongue, respectively. No blood was obtained in the bulla-like mass through aspiration. Hematoxylin and eosin (H&E)−stained sections showed extensive eosinophilic, amorphous, and acellular material deposition in the subepithelial tissue of those 2 samples (Figures 2A and 2B). We also observed an abundance of erythrocytes located under the epithelium of the purple-colored, bulla-like mass (see Figure 2A). Congo red staining showed that the eosinophilic, amorphous, and acellular material possessed brick-red coloration under conventional light microscopy (Figure 2C) and apple green birefringence under polarized light (Figure 2D). Immunohistochemical staining demonstrated that the λ light chain was positive, with extensively brown peroxidase staining (Figure 2E), but the κ light chain was negative in the submucosa of the purple-colored, bulla-like mass and nodule (Figure 2F). All these results confirmed the diagnosis of oral amyloidosis with the deposition of λ light chains.

Routine tests were conducted subsequently, and the hepatic function test demonstrated that total protein, globulin, and cholinesterase decreased to 52.7 g/L (60−83 g/L), 16 g/L (20−35 g/L), and 183 U/L (203−460 U/L), respectively. Renal function examination revealed that serum cystatin C and β_2-microglobulin increased to 1.91 mg/L (0.51−1.09 mg/L) and 8.01 mg/L (1−3 mg/L), respectively. Furthermore, routine urine testing revealed the presence of proteins in urine. The above results demonstrated that the patient had damaged hepatic and renal function. Considering that the patient had cutaneous hemorrhagic lesions and poor organ function, we suspected systemic amyloidosis, and further tests were performed. Serum protein electrophoresis (SPEP) revealed that monoclonal (M) protein was 11.6% (normal = 0) with immunoglobulin G (IgG), IgA, and IgM levels below the normal range. Immunofixation electrophoresis (IFE) confirmed that M protein was a λ light chain and that free λ light chain significantly rose to 16.7 mg/L (3.8−6.5 mg/L) in serum and 23.8 g/L (<0.05 g/L) in urine, whereas the free κ light chains dropped to 2.44 mg/L in serum (6.98−13 mg/L) and slightly increased to 0.0246 g/L (<0.02 g/L) in urine. The κ-to-λ ratio decreased to 0.15 (1.5−2.56) in serum. All of the above results confirmed that there was systemic involvement of light chain (AL) amyloidosis.

With regard to the abnormal M protein in serum, the patient was referred to a hematologist, and subsequent

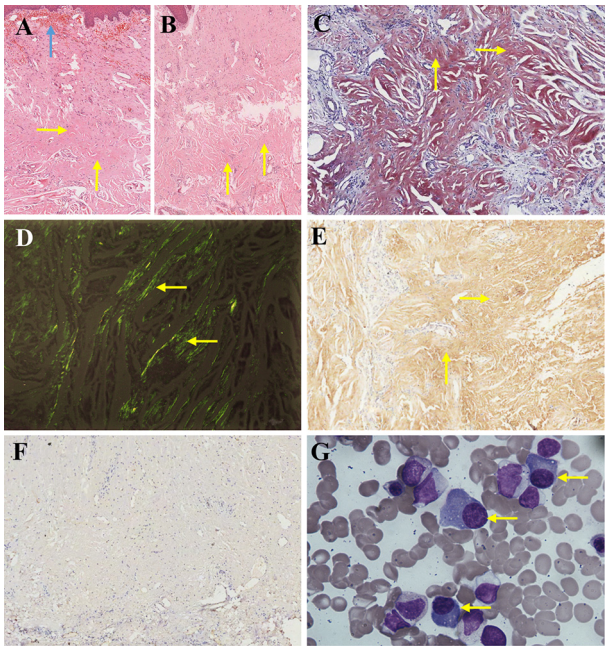

Fig. 2. Histopathologic examination and bone marrow biopsy. **(A, B)** Hematoxylin and eosin (H&E) staining of a purple-colored, bulla-like mass and a nodule: Abundant amorphous eosinophilic acellular deposition (*yellow arrows*; × 50 magnification) in the submucosa. Extravasated erythrocytes in the submucosa in a purple-colored, bulla-like mass (*blue arrow*; × 50 magnification). **(C)** Under conventional light microscopy, Congo red staining revealed diffuse brick-red staining in the submucosa of a purple-colored, bulla-like mass and a nodule (*yellow arrows*; × 50 magnification). **(D)** Under polarized light, Congo red staining showed apple green birefringence (*yellow arrows*; × 100 magnification) consistent with amyloid. **(E)** Positive immunohistochemical staining of the amyloid for λ light chains (× 50 magnification). **(F)** κ light chain was negative (× 50 magnification). **(G)** Bone marrow biopsy showed abnormal plasma cells of varying sizes and morphology *(yellow arrows)*, with basophilic cytoplasm and eccentric placed nuclei (× 1000 magnification). *A high-resolution version of panels A and B, C, E, and F of this image are available as eSlide: VM05607, VM05609, VM05610 and VM05613.*

bone marrow aspiration revealed proliferative and active bone marrow cells consistent with multiple myeloma (MM): The myeloid/erythroid ratio was as high as 4.65. Proliferative and active plasma cells accounted for 28.8%, and they were mainly plasmablasts (Figure 2G).

On the basis of the above evidence, the patient was diagnosed with MM-associated AL systemic amyloidosis. He was referred to the Department of Hematology at West China Hospital and received systemic treatment consisting of an MM-BD regimen (intravenous injection of both bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; and dexamethasone 20 mg/day on days 1, 2, 4, 5, 8, 9, 11, and 12). With regard to the oral lesions, the patient was prescribed mouth rinsing with 0.1% chlorhexidine to accelerate the healing process. Unfortunately, he died 3 months after the diagnosis.

DISCUSSION

MM is a malignant disease characterized by an abnormal plasma cell proliferation in bone marrow, and the proportion of plasma cell proliferation should be greater than 10%. The typical manifestations are known by the acronym CRAB—hypercalcemia, renal injury, anemia, and lytic bone lesions.[12] Abnormal plasma cells in the patient produce insoluble, abnormally folded amyloid precursor protein, the light chains (λ or κ light chain) of the immunoglobulin, which accumulate into systemic organs and tissues and are detected in the serum and urine to form AL systemic amyloidosis. A total of 10% to 15% of patients with MM may show complications of AL systemic amyloidosis, which should be diagnosed as MM-associated AL systemic amyloidosis, which is different from primary AL amyloidosis. Although primary AL amyloidosis is a disorder that is also mediated by excessive production and deposition of monoclonal immunoglobulin, bone marrow aspiration in patients with AL amyloidosis is usually reported to be normal, and no underlying diseases are found.[13,14] MM should be distinguished from other diseases that may induce AL amyloidosis, such as monoclonal gammopathy of undetermined significance (MGUS) and Waldenström macroglobulinemia. The plasma cell dyscrasia ratio in MGUS is less than 10%, and CRAB manifestations are absent in MGUS, both of which were different from the situation in our patient.[12] In Waldenström macroglobulinemia, monoclonal IgM in serum usually increases, and abnormal plasma cell−like lymphocytes infiltrate bone marrow.[15] However, in this patient, IgM was decreased in serum, and malignant plasmablasts, rather than plasma cell−like lymphocytes, were present in bone marrow.

Oral manifestations of AL amyloidosis are macroglossia, nodules, purple-colored bullae or blisters, ecchymoses, petechiae, and ulcers.[16,17] Our patient had almost all of the above-mentioned lesions. We performed a tissue biopsy and H&E and Congo red staining, which revealed oral amyloidosis. Although AL amyloidosis is the most common form of amyloidosis, other types of amyloidosis have been reported to exhibit oral manifestations. Amyloid fibrils of amyloid A amyloidosis (AA) and transthyretin amyloidosis (ATTR) are serum amyloid A protein and transthyretin, respectively. AA amyloidosis is usually secondary to chronic inflammatory conditions, such as rheumatoid arthritis, sarcoidosis, Crohn disease, and tuberculosis.[18] However, our patient did not have these diseases. Amyloid transthyretin amyloidosis rarely affects the mouth, and only macroglossia has been reported in a previous case report.[19] Therefore, immunohistochemistry staining for λ and κ light chains were performed and revealed that the amyloid fibrils were λ light chains. Amyloidosis cutaneous lesions are usually associated with macules suggestive of hemorrhage, which can be exacerbated by trauma. We inferred that these cutaneous lesions might result from the erythrocytes overflowing the blood vessel because of vascular fragility after the accumulation of amyloid fibril in the blood vessel wall. Our hypothesis was confirmed by H&E staining in the purple-colored, bulla-like mass, showing erythrocytes located below the epithelial layer outside blood vessels.

Amyloidosis can be local or systemic.[20] In this patient, the disease not only affected the oral cavity and skin but also injured the liver and the kidneys. Therefore, we concluded that the patient might have AL systemic amyloidosis. To confirm this, the patient underwent SPEP, serum IFE, and light chain protein assay to determine whether the light chains were present in the circulating blood. Finally, SPEP indicated the presence of M protein in blood and a decrease in IgA, IgM, and IgG to levels lower than normal. IFE and light chain assay confirmed that the abnormal protein in the patient's body consisted of λ light chains, consistent with the immunohistochemistry staining results in oral tissues. All of these results confirmed that the patient suffered from AL systemic amyloidosis.[13,14] Because systemic amyloidosis is usually secondary to malignant blood diseases, such as MM and macroglobulinemia, the patient was referred to a hematologist. This patient suffered from anemia, fatigue, and limited mobility and pain in the right upper arm; thus, the hematologist strongly recommended bone marrow aspiration, which revealed MM caused by the high proportion of plasma cell dyscrasia (28.8%). Therefore, the patient was finally diagnosed with MM-associated AL systemic amyloidosis.

Treatment for MM-associated AL systemic amyloidosis is similar to that for MM, and the aim is to decrease the abnormal plasma cells and to prevent light chains produced by these cells.[12,14,20] Therapy includes first-line treatment with peripheral stem cell transplantation and chemotherapy.[20] The prognosis largely depends on the stage of the primary disease. Serum β_2-microglobulin in our patient had increased to 8.01 mg/L, suggesting that he was in the late stage of

MM.[21] Peripheral stem cell transplantation was not appropriate because of the patient's hepatic and renal injuries, as well as his critical condition. The patient had a poor response to chemotherapy and suffered from dyspnea and dysphagia caused by macroglossia. He died 3 months after the diagnosis.

CONCLUSIONS

Oral lesions in MM-associated AL systemic amyloidosis may appear during the early stage of the disease. These abnormalities are easily perceived by patients, triggering a visit from the Department of Oral Medicine or Dermatology for medical advice. However, because of the rarity and complexity of this disease, clinicians may not take it into consideration in their differential diagnoses, leading to misdiagnoses. Therefore, we should be prudent in evaluating oral atypical, purple-colored, bulla-like masses, nodules, and submucosal/subcutaneous hemorrhagic lesions. Tests should be performed in a timely manner to exclude the possibility of MM-associated systemic amyloidosis because early diagnosis and treatment are critical to improving the prognosis.

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REFERENCES

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113:2386-2393.
2. Steel C, Mann L, Crosher R. Oral vesiculobullous lesions: consider the platelets. *Eur J Gen Dent*. 2014;3:167-169.
3. Rivera C, Torres Í. Haemorrhagic bullae in the oral mucosa with gingival bleeding. *BMJ*. 2017;359:j4476.
4. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115:168-186.
5. Francisconi CF, Caldas RJ, Oliveira Martins LJ, Fischer Rubira CM, da Silva Santos PS. Leukemic oral manifestations and their management. *Asian Pac J Cancer Prev*. 2016;17:911-915.
6. Grunwald MR, McDonnell MH, Induru R, Gerber JM. Cutaneous manifestations in leukemia patients. *Semin Oncol*. 2016; 43:359-365.
7. Shephard EA, Neal RD, Rose PW, Walter FM, Hamilton W. Symptoms of adult chronic and acute leukaemia before diagnosis: large primary care case-control studies using electronic records. *Br J Gen Pract*. 2016;66:e182-e188.
8. Ferguson AD, Johnston M, Leach IH, Allen BR. Angina bullosa haemorrhagica—a localized amyloidosis? *J Eur Acad Dermatol Venereol*. 2005;19:513-514.
9. Yayli S, Yayli AY. Angina bullosa haemorrhagica. *J Dtsch Dermatol Ges*. 2012;10:436-438.
10. Aškinytė D, Matulionytė R, Rimkevičius A. Oral manifestations of HIV disease: a review. *Stomatologija*. 2015;17:21-28.
11. Fatahzadeh M, Schwartz RA. Oral Kaposi's sarcoma: a review and update. *Int J Dermatol*. 2013;52:666-672.
12. Rajkumar SV. CME information: multiple myeloma: 2016 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2016;91:719.
13. Gillmore JD, Wechalekar A, Bird J, et al. Guidelines on the diagnosis and investigation of AL amyloidosis. *Br J Haematol*. 2015;168:207-218.
14. Gertz MA. Immunoglobulin light chain amyloidosis diagnosis and treatment algorithm 2018. *Blood Cancer J*. 2018;8:1-8.
15. Gertz M. Waldenström macroglobulinemia: 2015 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2015;90:346-354.
16. Deng J, Chen QM, Zeng X, Jin X, Ji P. Oral amyloidosis: a strategy to differentiate systemic amyloidosis involving the oral cavity and localized amyloidosis. *Oral Dis*. 2019;25:670-675.
17. Li Y, Liu N, Xu Y, et al. Widespread purple bulla-like masses of the oral mucosa. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114:552-557.
18. Cengiz MI, Wang HL, Yıldız L. Oral involvement in a case of AA amyloidosis: a case report. *J Med Case Rep*. 2010;4:200.
19. Cowan AJ, Skinner M, Berk JL, et al. Macroglossia—not always AL amyloidosis. *Amyloid*. 2011;18:83-86.
20. Bahlis NJ, Lazarus HM. Multiple myeloma-associated AL amyloidosis: is a distinctive therapeutic approach warranted? *Bone Marrow Transpl*. 2006;38:7-15.
21. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33:2863-2869.

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