Reminder of important clinical lesson

Paying more than lip service to an oral lesion: a case of plasmablastic lymphoma

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Summary

Plasmablastic lymphoma (PBL) is a variant of lymphoma originally described in the oral cavity of patients with advanced HIV. Our patient developed PBL despite well-controlled HIV and a CD4 count greater than 800 cells/ μ l. A drug interaction with an inhaled corticosteroid and ritonavir likely contributed to the development of this malignancy through increased immune suppression.

BACKGROUND

Oral lesions are common in persons with HIV and have a broad differential. Biopsy of rapidly growing, recurrent or otherwise atypical lesions is essential to rule out malignancy. Plasmablastic lymphoma (PBL) is a rare, but potentially devastating, cause of oral lesions in this population. Historically, HIV-associated PBL has been described in patients with CD4 counts less than 400 cells/ μ l. Recently, however, there has been increasing awareness that PBL can occur in persons with normal CD4 counts, particularly in the setting of other forms of immunosuppression. We report a case of PBL in a patient with a CD4 count of greater than 800 cells/ μ l. Exogenous Cushing's syndrome likely contributed to immunosuppression in this case. Drug interactions are an important cause of morbidity in persons with HIV. The presented case serves as a reminder that even inhaled medications can contribute to clinically significant drug interactions. Finally, the case serves as an opportunity to review how the physical presentation of Cushing's syndrome differs from lipodystrophy.

CASE PRESENTATION

A 43-year-old man with chronic HIV infection with a lesion on his left upper lip of 6-months duration presented to his general practitioner (figure 1A). The lesion was presumed to be a papilloma and was initially treated with cryotherapy. Despite treatment, the lesion continued to grow. The patient was referred to an otolaryngologist for further assessment. The patient also reported increasing proximal muscle weakness over the previous year with difficulty rising from the sitting position. He reported a 20 kg weight gain with the development of prominent centripetal obesity and a violaceous rash on his abdominal wall (figure 1B).

Regarding his history of HIV infection, he was initiated on combination antiretroviral therapy 6 years before his presentation. A CD4 count performed 1-month prior to presentation was 809 cells/ μ l. Viral load had been undetectable for over 5 years. Medical history also included hepatitis C virus infection, anal carcinoma secondary to human

papilloma virus infection that was cured with local resection, chronic obstructive pulmonary disease diagnosed 18 months prior and a recent diagnosis of type 2 diabetes mellitus. He reported daily marijuana use. His antiretroviral regimen included abacavir, lamivudine and atazanavir boosted with ritonavir. Other medications included citalopram, valproate, metformin, glyburide, risperidone, inhaled fluticasone and inhaled combination fluticasone-salmeterol.

On examination, he appeared chronically unwell. He was normotensive. Head and neck examination revealed moon facies and a prominent dorsal fat pad. A flesh-coloured lesion measuring 4 cm in diameter was present on the mucosal surface of his left upper lip. There was no thrush or other oral ulcerations. Abdominal examination revealed marked centripetal obesity with purple striae but no hepatosplenomegaly. There was marked muscle atrophy of the biceps and quadriceps bilaterally. Motor strength of the upper-extremity proximal muscles was 4/5 while the motor strength of the lower extremity proximal muscles was 3/5. Distal muscle strength was normal. There was no palpable lymph node enlargement. The remainder of the examination was normal.

INVESTIGATIONS

Investigations revealed a normal complete blood count, electrolytes and creatinine. Liver enzymes were increased: aspartate aminotransferase, 58 U/l (normal: 7–40 U/l), alanine transaminase, 66 U/l (10–45 U/l). The creatinine phosphokinase was in normal range. A diagnosis of Cushing's syndrome was suspected and was confirmed with hormonal assays. The adrenocorticotrophic hormone was less than 2 pmol/l (normal 4.4–18 pmol/l), an AM serum cortisol level was suppressed at 34 nmol/l (normal 140–700 nmol/l) and a 24-h urinary cortisol quantitation was also suppressed, suggestive of an exogenous steroid source of Cushing's syndrome.

The oral lesion was biopsied and pathology showed a dense infiltrate of medium to large atypical lymphocytes (figure 2A). Immunohistochemistry was consistent with a diagnosis of PBL (CD79+, CD138+, CD45– and CD20–).

Figure 1 (A) A flesh-coloured lesion measuring 4 cm in diameter on the mucosal surface of the left upper lip. (B) Violaceous striae on the abdomen.

In situ hybridisation for Epstein-Barr virus (EBV) was diffusely positive (figure 2B). Further staging with CT revealed supraclavicular nodes, which resulted in a clinical stage of IIAE.

DIFFERENTIAL DIAGNOSIS

Oral pathology is common in patients with HIV infection, especially in advanced stages of immunosuppression. Non-ulcerative mass lesions include both infectious and malignant aetiologies. Infectious aetiologies encompass human papilloma virus and mucosal abscesses secondary to bacteria and mycobacteria. Viral aetiologies and oral lesions secondary to *Treponema pallidum* infection are more

Figure 2 (A) H&E stain demonstrates medium to large cells with eccentrically placed nuclei and brisk mitotic activity ($\times 600$). (B) In situ hybridisation of Epstein-Barr virus positive in the malignant cells ($\times 600$).

likely to present with ulcerative lesions. Malignant aetiologies include squamous cell carcinomas, Kaposi sarcoma, diffuse large B cell lymphoma, Burkitt's lymphoma, natural killer cell lymphoma and plasmablastic lymphoma.¹ Biopsy of lesions is needed for diagnosis.

TREATMENT

The patient was treated with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone). The patient's inhaled medications were changed to beclomethasone and formoterol, which are not metabolised through the cytochrome P450 3A4 pathway unlike fluticasone.

OUTCOME AND FOLLOW-UP

After one cycle, there was a visible decrease in the size of the lip lesion. Six cycles of CHOP were planned; however, the treatment was halted after three cycles, due to poor tolerance. Nonetheless, the patient achieved a complete remission, and remained in remission at last follow-up. The patient's proximal muscle weakness, central obesity and moon facies slowly resolved after his fluticasone was

discontinued. His diabetes has become easier to control, but did not remit.

DISCUSSION

PBL is a rare form of HIV-associated non-Hodgkin's lymphoma (NHL), which typically presents with oral lesions, and tends to occur in patients with low CD4 counts and high viral loads.² Patients with PBL have an insidious presentation, whereby the lesion is often mistaken for an oral abscess.¹ There is a strong association with prior EBV infection as demonstrated by the in situ hybridisation for EBV in this patient.

A review of 191 consecutive patients with HIV-NHL from 1984 to 1997 demonstrated that only 2.6% of these lymphomas were PBL.³ One review of 112 cases of PBL in HIV-positive patients found the condition developed after a median duration of 5 years (range, 0–20) after HIV diagnosis. The median CD4 count was 178 cells/ μ l (range 10–498 cells/ μ l).⁴ Of those affected, 88%, were men. Although a majority of PBLs develop in the oral cavity, other primary sites included the gastrointestinal tract (13%), lymph nodes (6%) and other non-oral sites (23%).⁴ In another review, similar data were found and the average reported viral load was 86 884 copies/ml (range, undetectable—750 000 copies/ml).¹

Although PBL is classified by the WHO as an NHL occurring more specifically in HIV-positive individuals, recent reports suggest that it is becoming more prevalent among patients who are HIV negative.⁵ For instance, a recent review reported that approximately 30% of the patients who developed PBL did not have HIV and a quarter of these patients had another form of immunosuppression including solid organ transplantation or receipt of corticosteroids, azathioprine or chemotherapy.⁵ We postulate that, in this case, the additional immunosuppression from the inhaled steroids resulting in an iatrogenic Cushing's syndrome contributed to the development of PBL.

This case highlights the need for careful monitoring of potential interactions between antiretroviral drugs and other commonly prescribed medications. Ritonavir is a potent inhibitor of cytochrome (CY) P450 3A4. The two corticosteroids formulated in combination inhalers, fluticasone (with salmeterol) and budesonide (with formoterol), are both extensively metabolised by CYP 3A4. Concurrent administration with a CYP 450 3A4 inhibitor such as ritonavir can markedly increase serum levels of steroid. This increased level of corticosteroid has been reported to lead to adrenal suppression and Cushing's syndrome as in the case of our patient.⁶ Our patient's

physical findings of abnormal fat distribution may have been mistaken for lipodystrophy; however, increased body weight, proximal myopathy and cutaneous changes such as striae are characteristic of Cushing's syndrome and are not described in HIV-related lipodystrophy.⁷

Learning points

- Oral lesions in patients with chronic HIV should always be investigated and malignancy should be included in the differential.
- Plasmablastic lymphoma is an aggressive HIV-associated lymphoma that classically presents as an oral lesion.
- Drug interactions are an important cause of morbidity in patients on antiretroviral therapy. Ritonavir can increase systemic levels of inhaled steroids leading to exogenous Cushing's syndrome.
- Lipodystrophy and Cushing's syndrome both cause central obesity. However, Cushing's syndrome also causes moon facies, dorsal fat pad, striae and proximal myopathy, not seen in lipodystrophy.

Competing interests None.

Patient consent Obtained.

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