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Pediatric oral Epstein-Barr virus associated self-remitting CD30+ lymphoproliferative disorder: A distinct entity☆

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ABSTRACT

Epstein-Barr virus (EBV) has a well-known association with lymphoproliferative disorders of B and T cell origin. EBV-related B cell lymphoproliferative disorders include Hodgkin and Burkitt lymphomas, lymphomatoid granulomatosis, EBV positive diffuse large cell B cell lymphoma of the elderly, as well as B cell lymphomas associated with solid organ transplantation and methotrexate use. EBV-related T cell disorders are primarily represented by NK/T- cell lymphoma. In a subset of patients, EBV has been implicated in CD30 positive B cell lymphoproliferative disorders of the oral mucosa falling under the rubric of the mucocutaneous ulcer of the oral cavity. We previously reported on an index series of endogenous CD30 positive T cell lymphoproliferative disorder of the oral cavity resembling borderline type C lymphomatoid papulosis. The clinical manifestation of type C oral lymphomatoid papulosis is that of a recurrent self-remitting ulcer of the oral mucosa, which histologically resembles anaplastic large cell lymphoma. Such cases can be misdiagnosed as aggressive lymphoma leading to unnecessary treatment with aggressive chemotherapeutic regimens. Whereas none of the patients in our index series exhibited EBV positivity, here we discuss a very unique example of a 14-year-old girl diagnosed with EBV positive CD30 positive lymphoproliferative disorder strongly resembling the cases of intra-oral type C lymphomatoid papulosis. The patient was initially diagnosed by a senior hematopathology consultant as having EBV positive aggressive NK/T-cell lymphoma. The significance of raising physician awareness regarding pediatric oral EBV associated CD30 positive lymphoproliferative disease of the oral cavity lies in preventing inadvertent exposure to toxic chemotherapeutic agents intended for treatment of aggressive look-alikes, namely anaplastic large cell lymphoma. Additionally, we include a literature review of similar reports of pediatric intra-oral EBV positive CD30 positive T cell lymphoproliferative disease.

1. Introduction

Oral lymphomatoid papulosis (LyP), a CD30 positive subtype of lymphoproliferative disorder (LPD), is defined by a benign, indolent, self-resolving clinical nature. As a CD30 positive LPD (LPD30), it falls under the overarching nosologic designation of eosinophilic ulcer of the oral mucosa (EUOM) [1,2]. As described by the authors in a previous publication, LyP classically manifests as a cutaneous exanthem, but there is a growing recognition of a LyP variant localizing to the oral mucosa [2-12].

LyP poses a unique challenge for the diagnosing physician, in that its histologic and morphologic presentation closely resembles other more aggressive LPD30. LyP is often mistaken for aggressive T-cell lymphomas, particularly anaplastic large cell lymphoma. The authors previously reported on five patients with type C oral LyP, four of whom received an initial diagnosis of aggressive peripheral T-cell lymphoma necessitating later diagnosis revision to LyP due to spontaneous resolution of the lesions [12].

As part of the investigation into type C oral LyP, the authors identified an adolescent girl who despite conforming to criteria for type C oral LyP, was an outlier in both her young age, as well as Epstein-Barr virus (EBV) positivity among the biopsied lesions. Further exploration of the literature revealed that this pattern has previously been reported in a handful of pediatric patient cases. Like many adult patients suffering from type C oral LyP, she was originally thought to have aggressive peripheral T-cell lymphoma by a leading authority on LPD. A second opinion rendered the final diagnosis of EBV associated CD30 positive LPD, consistent with type C LyP.

☆ Declaration of interest: none.

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The purpose of this paper is twofold. The first is to propose that pediatric EBV associated oral LyP may be emerging as a unique entity, distinct from oral LyP. This conclusion is supported by its propensity for a younger patient population and is bolstered by the growing number of examples in the literature that share this common line of pathogenesis. The second purpose is to increase awareness among physicians of this entity in order to avoid misdiagnosis and inadvertent treatment of patients with toxic chemotherapeutic agents, particularly in the susceptible pediatric community.

2. Results

2.1. Patient case

A 14-year-old girl presented to the emergency department with a painful sore on the right lower lip mucosa accompanied by facial swelling. The lesion had appeared one month prior as a "small blister," which was treated with antibiotics without improvement. The patient also reported a history of small sores in her mouth in different areas at different times, of short duration and without swelling. Upon examination of this lesion, there was prominent surrounding swelling of the right lower lip, with induration of the lip and deep soft-tissues infero-lateraly. There was a broad swatch of necrotic tissue on the mandibular buccal vestibule about 1 cm wide (Fig. 1). Biopsy led to an initial diagnosis of extranodal NK/T-cell lymphoma nasal type. A second opinion revised the diagnosis to EBV associated LPD30, consistent with type C LyP. At the two week follow up, the broad swatch of necrosis had been replaced by granulation tissue. At the four week follow up, a second lesion appeared anterior to the former. A third lesion appeared at six weeks post-presentation, adjacent to the other two and with increasing pain. The new lesions were described by the patient as having started out as "bubbles" that burst, leaving white fluid and blood. The patient was treated with antibiotics for a super-infection. A second biopsy at week eight led to a third diagnosis revision to atypical EBV-positive T-cell infiltrate suspicious for extranodal NK/T-cell lymphoma, nasal type. By week 10, the lesions had begun to heal, with all 3 ulcers regressing by week 12 post-presentation. The patient reported no recurrences for the following two years, whereas during the third year the patient reported experiencing a brief self-limiting ulcer. The indolent course, spontaneous regression and review of histology point to a final diagnosis of EBV associated LPD30, most consistent with type C LyP. It is unclear whether medication the patient was taking to treat her bipolar illness contributed to immune dysregulation resulting in reactivation of EBV within infected T-cells and accounting for the lymphomatoid quality of the infiltrate.

2.2. Light microscopic findings

The biopsy was sent for a second opinion to one of the authors, for which the diagnosis "Epstein-Barr virus associated indolent CD30-positive lymphoproliferative disease consistent with intraoral type C lymphomatoid papulosis as a distinct subset of eosinophilic ulcer of the tongue" was rendered. In particular, the biopsy showed a psoriasiform pattern of epithelial hyperplasia. There was moderate spongiosis with exocytosis of lymphocytes and histiocytes into the squamous epithelium. An extensive superficial and deep lymphohistiocytic infiltrate accompanied by many eosinophils was observed (Fig. 3). The histiocytes included a few multinucleated forms. There was an extensive zone of necrosis which was likely in part an ischemic based phenomenon based on the presence of vascular thrombosis (Fig. 2). The lymphocytes also included a subset that had a somewhat histiocytoid appearance but with enhanced atypia relative to the background macrophages. These cells were in the 20 to 30-micron size range exhibiting conspicuous macroeosinophilic nucleoli (Fig. 4). There was binucleation and multinucleation amidst these larger atypical cells. Accentuation around vessels defining a lymphomatoid vascular reaction was also identified.

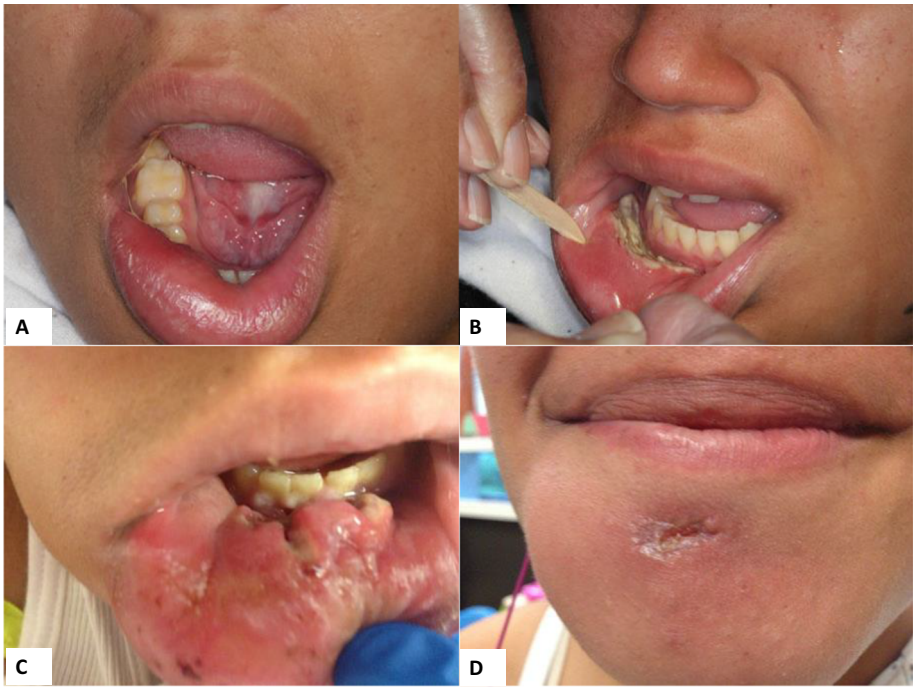

Fig. 1. The patient developed progressive ulceration of sublingual area and the inner mucosal surface of the lip.
A & B: Evolution phase.
C & D: Resolution phase (two and three months, respectively).