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Case Report

Pathology Section

Incidental Detection of Hairy Cell Leukaemia with Herpes Simplex Virus (HSV) Related Lip Ulcer Mimicking Carcinoma

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ABSTRACT

Hairy cell leukemia is a chronic lympho-proliferative disease. It is indolent but progressive in nature. It arises from B-cell lineage. We report an incidentally detected case of Hairy Cell Leukaemia (HCL) in a 55-year-old male patient with Herpes simplex virus (HSV) - related lip ulcer mimicking squamous cell carcinoma. Clinically the patient presented with lip ulceration without pain. He was found to have moderate hepatosplenomegaly and pancytopenia on general examination. Bone marrow aspiration and flow cytometric immunophenotyping revealed HCL. The oral lesion resolved after antiviral therapy. The intriguing possibility of a combined pathogenesis for the two disorders is considered, as HCL is known to be associated with immunosuppression, second malignancies and the production of cytokines promoting epithelial growth.

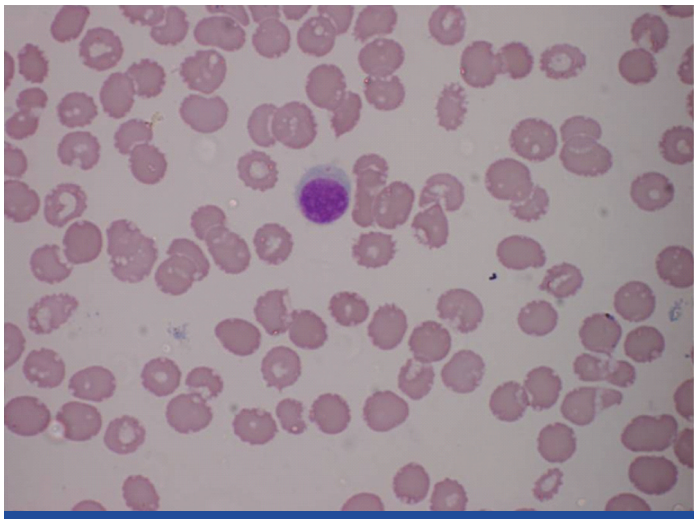
Keywords: Immunosuppression, Oral premalignant lesions, Pseudoepitheliomatous hyperplasia

CASE REPORT

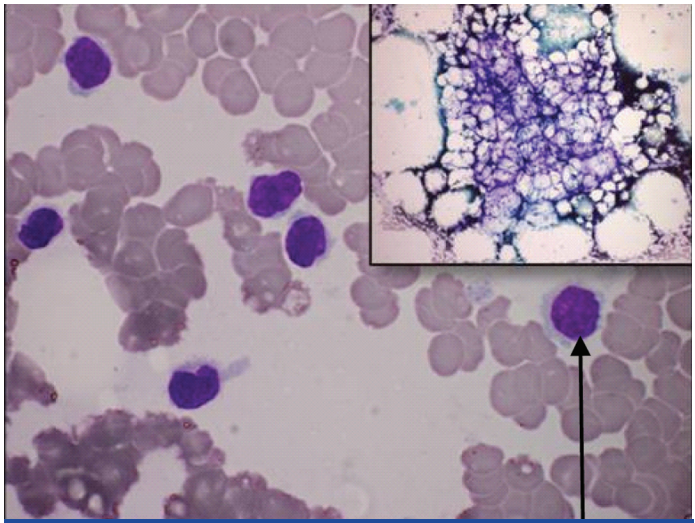
A 55-year-old male presented to Otolaryngology OPD with a one-month history of a non-healing ulcer on the mucosal aspect of the upper lip measuring 2x2 cm. He had no history of smoking or use of tobacco. A clinical suspicion of malignancy was kept and biopsy was done to confirm the diagnosis. Biopsy comprised of multiple fragments, poorly oriented with ulceration of epithelium. There was irregular hyperplasia with jagged extensions into the subepithelium. The keratinocytes showed nucleomegaly, prominent nucleoli and abundant eosinophilic cytoplasm with focal keratinization and binucleation. High-grade nuclear atypia was not seen; however, mitotic figures were increased focally. The histological possibilities of pseudoepitheliomatous hyperplasia versus a minimally-invasive, well differentiated squamous cell carcinoma were considered and communicated to the clinical team while deeper level sections were ordered.

The patient was referred to Radiotherapy and Oncology where he was admitted for work-up of suspected malignancy. On local examination, a small, relatively superficial lesion with surrounding erythema and induration was noted. Physical examination revealed pallor along with liver and spleen palpable 4 cm and 2 cm below the respective costal margins. There was no palpable regional or other lymphadenopathy. A Complete Blood Count (CBC) showed pancytopenia: haemoglobin (Hb) 7.9 gm/dl with total leukocyte count (TLC) 2.8x10^9/L and platelet count 122x10^9/L. The peripheral smear revealed 40% neutrophils, 52% lymphocytes and 3% eosinophils with an occasional nucleated red cell [Table/Fig-1].

Haematology consultation was sought and a Bone Marrow (BM) examination was done to evaluate the cause of pancytopenia and hepatosplenomegaly. The aspirate smears showed fat-rich paucicellular particles with reduced haematopoietic elements and 81% abnormal lymphoid cells. These cells had round to oval nuclei with bland nuclear chromatin, occasional small nucleoli and moderate to abundant pale blue cytoplasm with indistinct or hairy cytoplasmic margins. The BM biopsy was mildly hypocellular with extensive lymphoid cell infiltrates virtually replacing normal haematopoiesis [Table/Fig-2]. The lymphoid cells showed round nuclei with a moderate amount of clear cytoplasm and prominent



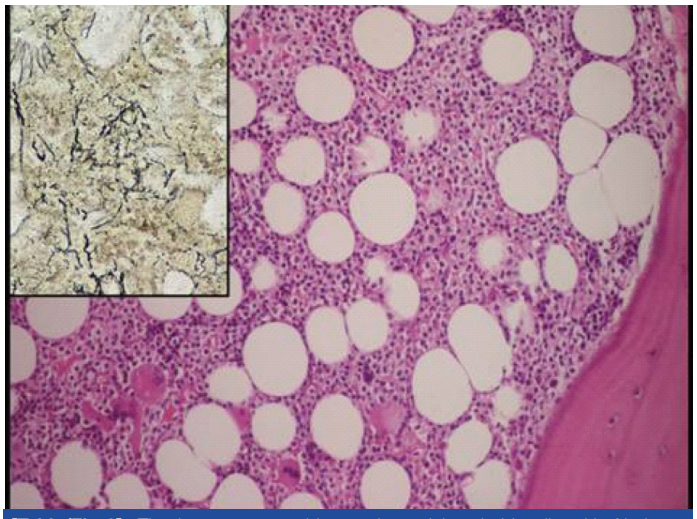
[Table/Fig-1]: Peripheral smear showing atypical lymphocytes (Leishman; x400).



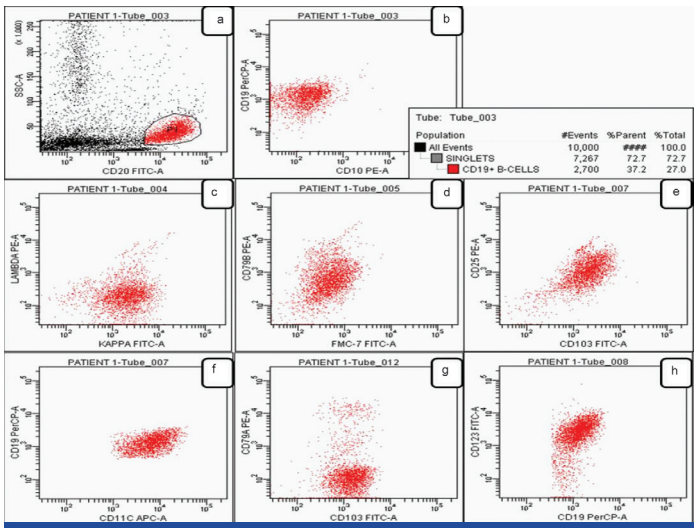
[Table/Fig-2]: The bone marrow aspirate smears showed fatty paucicellular particles. (MGG stain, 40X).
Inset Abnormal lymphoid cells showing fried egg appearnce (shown by arrow) comprised 81% of all marrow cells. (MGG stain, x400).

cytoplasmic margins (fried-egg appearance) [Table/Fig-3]. The reticulin stain showed pericellular pattern, grade 2 (Bauermeister grading, 0-3) [Table/Fig-3]. Flow cytometry of the bone marrow aspirate revealed ~37% CD19 positive B-lymphoid cells with moderate side scatter that expressed bright CD20 along with CD25, CD103 and CD11c [Table/Fig-4] and were negative for CD3, CD5, CD23 and CD10. The morphological and immunophenotypic findings thus confirmed a diagnosis of HCL.

The patient was given a trial of oral acyclovir (15 mg/kg/day for 7 days) that led to near-complete resolution of the lip lesion over 3 weeks. The deeper level sections of the biopsy did not reveal any definite malignancy. Immunohistochemistry on the paraffin block was positive for Herpes Simplex Virus (HSV). He was treated for HCL with cladribine (2-chlorodeoxyadenosine) for a week. Subsequently, his TLC dropped further to 0.4 $x10^9$/L with an absolute neutrophil count of 0.1 $x10^9$/L. He received granulocyte colony stimulating factor (G-CSF). However, he developed a bacterial middle ear infection which rapidly spread systemically leading to septic shock causing death within a month of diagnosis.



[Table/Fig-3]: The bone marrrow biopsy showed lymphoid cells with fried-egg appearance and corresponding reduction in hematopoietic elements (Hematoxylin and Eosin, x200).
Inset: The marrow reticulin content was increased (Gordon and Sweet's silver stain, x400).



[Table/Fig-4]: Flow cytometric immunophenotyping revealed ~37% CD19 and CD20 (a,h) - positive B-lymphoid cells with moderate side scatter (b) (almost equivalent to that of normal monocytes). These cells expressed CD20, CD25, CD103 (e,g) and CD11c (f) and showed kappa light chain restriction (c,d).

DISCUSSION

Hairy cell leukaemia (HCL) is an uncommon chronic lymphoproliferative disorder that typically presents with pancytopenia and splenomegaly. Mucocutaneous lesions like erythematous maculopapules, scleroderma and pyoderma gangrenosum have only rarely been described in these patients [1,2]. Hairy Cell Leukaemia (HCL) accounts for ~2% of lymphoid leukaemias. Patients typically present with splenomegaly and pancytopenia with marked monocytopenia [3]. The spleen is palpable in ~80% of cases, and is >5 cm to massive in size below left costal margin in 60% [4]. Some patients, like ours, may be completely asymptomatic despite the organomegaly and cytopenias and may come to clinical attention for completely unrelated complaints or following a routine blood count. Late presentations are especially common in Indian patients due to both difficulties in accessing health care facilities leading to increased mortality.

HCL patients have an increased incidence of various bacterial, fungal and protozoal infections attributable in part to granulocytopenia, monocytopenia, poor granulocyte reserve and abnormal mobilization, T-cell dysfunction and decreased numbers of dendritic cells and antigen presenting cells [4,5]. A specific increase in the incidence of HSV infection/reactivation has not been described in the english medical literature to the best of our knowledge. However, one study found HSV replication, supported only by peripheral blood mononuclear leukocytes from patients with HCL and not those with chronic lymphocytic leukaemia, acute lymphoblastic leukaemia or other non-Hodgkin lymphomas [5]. Rohr et al., in their clinical trial reported the appearance of HSV with HCL in only three cases [6]. However, any case report which establishes such co-occurrence using detailed evidence based examination with aid of flow cytometric immunophenotyping and smears studies, have not been published yet.

Apart from the immunosuppressive influences listed above, a significantly higher incidence of second malignancies has been observed in HCL patients [7]. Thus, it is interesting to speculate on a possible common pathogenesis for the two lesions, however no possible correlation of HSV as an independent factor for causation of HCL was found. It is merely a chance occurrence. Mutations in the p53 tumour suppressor gene were observed in nearly 28% of HCL patients in one study [8] which are also well described in oral and oropharyngeal carcinomas and premalignant lesions [8]. This suggests that there may hence be a common event linking the oral lesion and HCL [9].

Many cytokines are released by hairy cells including TNF-α, IL-4, IL-6, IL-2 and IFN-α [10] which are known to participate in autocrine and paracrine regulation of growth, differentiation and migration of malignant cells. These second mediators are, however, also known to stimulate epithelial cell proliferation *in vitro* [11]. In addition, the pathological and iatrogenic immunosuppression caused by HCL and its therapy, specifically the loss of cell-mediated immunity, may have also played a role [12,13].

Recent reports document the presence of BRAF gene mutations in virtually all HCL [14] which also occur in 3% of head and neck squamous cell carcinomas [8]. Although a major role is as yet undescribed in oral premalignant lesions, they do occur in colonic serrated adenomas and may therefore play a role in the progression of malignancy [15]. Curiously, the development of squamoproliferative lesions including Squamous Cell Carcinom (SCC) and keratoacanthomas is an adverse effect increasingly noted in melanoma patients treated with BRAF inhibitors [16].

CONCLUSION

The oral lesion and HCL in our patient are whether unrelated chance occurrences, or share a common pathogenesis remains conjectural. However, what is clear is that the work-up of a suspected malignancy prompted a detailed haematological evaluation that unmasked an indolent lymphoproliferative disorder. This patient thus illustrates yet another dramatic and unique presentation of the enigmatic HCL to the interdisciplinary

team of the anatomic pathologist, haemato-pathologist and the haematologist-oncologist.

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