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Cartilage hair hypoplasia with cutaneous lymphomatoid granulomatosis

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Summary

Cartilage–hair hypoplasia (CHH) is an autosomal recessive chondrodysplasia characterized by short-stature, sparse hair and impaired cellular immunity. We describe a young girl who was diagnosed with CHH based on the findings of recurrent infections, short stature with metaphyseal chondrodysplasia, and a confirmed bi-allelic *RMRP* gene mutation. At 13 years, the patient developed an Epstein–Barr Virus (EBV)-driven lymphoproliferative disorder involving the lung, which responded partially to chemotherapy. Simultaneously, she developed multiple indurated plaques involving the face, which had histological findings of granulomatous inflammation and EBV-associated low-grade lymphomatoid granulomatosis. The patient received a matched unrelated peripheral blood stem cell transplant at 15 years and her immunological parameters and skin lesions improved. Lymphomatoid forms of granulomatosis and cutaneous EBV-associated malignancies have not been previously described in CHH. This case highlights the possibility of EBV-associated cutaneous malignancy in CHH.

Comment [Q2]: AU Query: CED uses 'z' spelling.

Cartilage–hair hypoplasia (CHH) is a rare autosomal recessive metaphyseal chondrodysplasia caused by mutations of the untranslated *RMRP* gene, which encodes for the RNA component of the mitochondrial RNA processing (RMRP) endoribonuclease. CHH is characterized by short stature with other skeletal abnormalities, fine sparse hair, and abnormal immune system function (immune deficiency) that can lead to recurrent infections.[1] Granulomatous inflammation is described in patients with various forms of primary immunodeficiencies including CHH; however, lymphomatoid granulomatosis (LG) has not been reported in patients with CHH. LG is a rare Epstein–Barr Virus (EBV)-driven B-cell lymphoproliferative disorder that most frequently involves the lungs but may also involve the skin and central nervous system. LG is graded from 1 to 3 according to the number of EBV-positive cells in a high-power field (HPF).[2] We describe a girl with CHH and an EBV-driven lymphoproliferative disorder involving the skin and the lungs.

Report

Comment [Q3]: AU Query: Concise reports have only the single heading of 'Report' so all other headings have been deleted.

A 13-year-old girl with CHH presented with a 4-month history of asymptomatic purple plaques and nodules on her nose, upper lips and chin (Fig. 1a b). She had been born healthy to unrelated white parents and there was no significant family history. The patient developed recurrent infections in her first year of life and severe chicken pox at the age of 7 years, resulting in varicella pneumonitis and bronchiectasis.

Comment [Q4]: AU Query: CED prefers 'white' to 'Caucasian'.

When the patient was 11 years old, the diagnosis of CHH was suggested as she had recurrent severe chest infections, short stature (height persistently < 0.4 percentile) and the radiological finding of

metaphyseal chondrodysplasia in the long bones. Immunological studies revealed a lower than normal CD8 count for age, indicating T-cell lymphopenia: T cell CD3+: 0.56×10^9/L (range $0.8–3.5 \times 10^9$/L), CD3+CD4+: 0.46×10^9/L ($0.4–2.1 \times 10^9$/L), CD3+CD8+: 0.08×10^9/L ($0.2–1.2 \times 10^9$/L); B cell CD19+: 0.18×10^9/L ($0.2–0.6 \times 10^9$/L); and natural kiler cell CD16+CD56+: 0.15×10^9/L ($0.07–1.2 \times 10^9$/L). In addition, she had intermittent neutropenia and immunoglobulins were normal. Genetic analysis revealed a compound heterozygous mutation, g(4C>T) and g(242A>G), in the RNAse mitochondrial RNA processing endoribonuclease gene (*RMRP*), confirming the diagnosis of CHH. On dermatological examination, the rest of her skin, hair and nails were normal. Skin biopsy from a facial lesion showed granulomatous dermatitis composed of lymphocytes and histiocytes with a few epithelioid granulomas. The lesions did not respond to superpotent topical steroids (clobetasol proprionate cream), and the patient was lost to dermatological follow-up.

At the age of 14 years, multiple progressive round lesions in both lungs were noted on a computed tomography scan of the thorax and a biopsy of the right anterior lung mass showed EBV-driven diffuse large B-cell lymphoma (Fig. 2). She received treatment with modified lymphoma protocol (GRAB) with rituximab for 6 months. An initial response to chemotherapy was seen, but residual lung lesions remained at the end of treatment, which on further resection showed complete necrosis negative for EBV. The patient was re-referred to dermatology at 14 years as the skin lesions continued to increase despite chemotherapy.

Comment [Q5]: AU Query: Why did the patient present at the age of 14 for the CT? And to what department?

Comment [Q6]: AU Query: Please give the drugs used in GRAB.

Comment [Q7]: AU Query: No resection was mentioned earlier; is this a biopsy?

At presentation, the patient was found to have extensive purple plaques and nodules infiltrating deep into the subcutis on her nose, nasolabial folds, cheeks, upper lip and chin (Fig. 1c,d). Histological examination of a skin biopsy from a chin nodule revealed a dense, diffuse, angiocentric and angioinvasive chronic inflammatory infiltrate of the reticular dermis, mainly composed of mature lymphocytes and histiocytes with some epithelioid granulomas and Langhans type giant cells. Scattered larger atypical lymphoid cells were also noted (Fig. 3). *In situ* hybridization (ISH) for EBV-encoded RNA (EBER) (Fig. 3) showed positivity only in the large cells (< 5 EBV-positive lymphoid cells per HPF).Retrospective ISH studies with EBER of the original skin biopsy showed similar findings. Based on these features, the diagnosis of grade 1 EBV-driven LG of the skin was made in this patient with known CHH previously treated for grade 3 pulmonary LG.

At 15 years, the patient underwent a successful matched unrelated peripheral blood stem cell transplant for the management of immunodeficiency, which also led to marked improvement in her skin lesions. (Fig. 1e, f)

To our knowledge, his is the first report of cutaneous LG described in CHH, reinforcing that EBV-associated granulomas should be considered in cutaneous lesions of patients with immunodeficiency. CHH is a primary immunodeficiency syndrome with impairment of cellular immunity in > 85% of patients, and in a minority humoral immunity can also be affected. Mortality is high in patients with CHH because of their defective immunity and frequent infections. Patients with CHH also have a seven-fold increased risk of cancer.[1] The most frequent cancer diagnoses have been non-Hodgkin lymphoma of B-cell origin and basal cell carcinoma.[3]

LG is a rare EBV-driven B-cell lymphoproliferative disorder with reactive T cells, primarily involving the lung, but also the skin, kidney and brain. LG usually occurs in middle-aged adults and is only rarely seen in childhood.[2] In a review of LG in 49 children aged 0–18 years, only 11 had cutaneous involvement. LG mostly occurs in immunocompromised patients, indicating that immunodeficiency plays a role in its aetiology.[4] The classic histopathological features include angiocentric and angiodestructive lymphoid infiltrate with EBV-positive large atypical B cells and a prominent population of small reactive T cells and necrosis.[2]

Granulomatous inflammation has been described in patients with immunodeficiencies and is thought to be a manifestation of immune dysregulation. Tacke *et al*. found epithelioid granulomas in 4 of their 21 patients with CHH.[5] One of the four patients showed positivity for ISH with EBER within one skin biopsy specimen; however, the EBV screening before and after this biopsy were all negative, and this finding was deemed coincidental and unrelated to the pathogenesis of granulomas. Three of these four patients had significant improvement after initiation of treatment with anti-tumour necrosis factor-α monoclonal antibody, and in two patients, there was complete regression of the lesions following immune reconstitution after allogenic haematopoietic stem cell transplant. Therefore, recovery of immune function might resolve both the unidentified infections and correct immune dysregulation.[5]

Our paediatric case demonstrates a rare association of cutaneous LG with CHH. We conclude that EBV-driven lymphoproliferative disorder should be considered when patients with CHH develop granulomatous lesions. EBER staining is essential in this scenario to exclude LG, as the histopathology of most of these granulomas can appear benign.

Learning points

- CHH is an autosomal recessive disorder characterized by short stature, sparse hair and immunodeficiency due to mutations in the *RMRP* gene.
- CHH has a wide spectrum of clinical manifestations.
- Mortality is high, owing to recurrent infections and malignancies.
- The extent of the immunodeficiency in CHH is highly variable, ranging from mild to severe, and can affect both T-cell and humoral immunity.
- LG is a rare EBV-driven B-cell lymphoproliferative disorder primarily involving the lungs and usually occurs in middle-aged adults and rarely seen in childhood.
- EBV-driven lymphoproliferative disorders should be considered during evaluation of patients with immunodeficiencies, and granulomatous inflammation and EBER staining is necessary to establish the diagnosis.

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Figure 1 (a,b) Erythematous slightly purplish plaques and nodules with mild atrophy involving the nose, upper lips and chin; (c,d) worsening of the skin lesions despite chemotherapy, with extensive plaques involving the nose and extending to the cheeks, lips and the chin; (e,f) improvement of the skin lesions at (e) 4 and (f) 7 months following peripheral blood stem cell transplant .

Figure 2 (a) Lung biopsy showed nodules that were partially necrotic and composed of dense aggregates of large atypical lymphoid cells (haematoxylin and eosin, original magnification × ???). (b) *In situ* hybridization with an Epstein–Barr virus (EBV) early RNA (EBER) probe, showing that almost all the cells were positive for EBV.

Figure 3 (a–c) Skin biopsy from a chin plaque showing (a) dense and diffuse chronic inflammatory infiltrate of reticular dermis composed of nonatypical lymphocytes, histiocytes and scattered larger lymphoid cells; (b) focal localization of epithelioid granulomas; (c) angiocentric and angioinvasive infiltrate. Haematoxylin and eosin, original magnification (a) × ???; (b) × ???; (c) × ???. (d) *In situ* hybridization with tan Epstein–Barr virus (EBV) early RNA (EBER) probe, showing occasional EBV-positive cells.

Comment [Q8]: AU Query: Please give original magnification.

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