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CASE REPORT

Orbital lymphomatoid granulomatosis – a rare cause of proptosis

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Abstract A 1-year-old girl with unilateral proptosis was found to have primary orbital lymphomatoid granulomatosis – a condition rarely occurring in children. This multisystem angiocentric, angiodestructive, lymphoproliferative disease typically involves the lungs, with ocular involvement being extremely uncommon. Our case serves to illustrate the imaging findings of this unusual condition and highlight a rare cause of proptosis.

Keywords Lymphomatoid granulomatosis · Proptosis · Epstein-Barr virus · Child · Magnetic resonance imaging

Introduction

Lymphomatoid granulomatosis is a rare, progressive lymphoproliferative disorder driven by Epstein-Barr virus, in which abnormal cells directly accumulate in extranodal tissues as infiltrative masses with destruction of blood vessels [1]. The condition is uncommon in children [2, 3].

We report a case of primary orbital lymphomatoid granulomatosis in a 1-year-old girl – a unique presentation of an unusual condition – and focus specifically on the MRI findings.

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Case report

A 1-year-old girl, who had been previously well, presented to the ophthalmology outpatient clinic with a 2-week history of right eye proptosis. On examination, there was right-sided proptosis with periorbital soft tissue swelling and erythema, as well as conjunctival chemosis. Right eye movements were restricted in all directions. The remainder of her clinical examination was normal. As there was clinical concern about an intraorbital mass, she was referred for MRI.

MRI revealed a heterogeneous mass located within the medial aspect of the right orbit causing proptosis, with distortion of the right globe and stretching of the optic nerve. The periphery of the mass was T1 isointense and T2 hypointense to muscle, with an area of central breakdown (Fig. 1). There was peripheral enhancement of the solid component implying central necrosis (Fig. 1). Diffusion-weighted imaging revealed marked restriction of the solid component, with corresponding low values on apparent diffusion coefficient (ADC) maps suggestive of a highly cellular mass.

There was associated destruction of the medial orbital wall, extension into the ethmoid air cells and displacement of the nasal septum to the right. In addition, there was intracranial extension with an associated right frontal meningeal reaction (Fig. 1).

In view of the T2 hypointensity, restricted diffusion and destructive nature, the mass was interpreted as a cellular tumor. The differential diagnosis considered included B-cell lymphoma, orbital pseudotumor and rhabdomyosarcoma (although these are rarely T2 hypointense). The possibility of tuberculosis was also entertained in view of the T2 signal and peripheral enhancement.

The girl's chest radiograph was normal as was her blood work, which revealed no underlying immunodeficiency. Her bone marrow aspirate showed focal features suggestive of involvement by lymphoma, but the trephine (core biopsy of the iliac crest containing marrow) was clear.

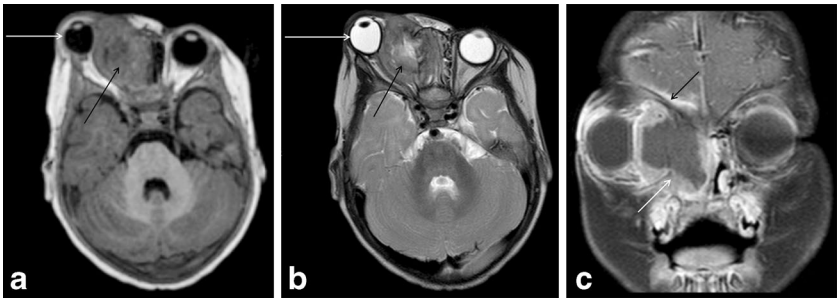

Fig. 1 Brain MRI in a 1-year-old girl at presentation. Axial T1-W (**a**) and T2-W (**b**) images reveal a heterogeneous, predominantly T1 isointense, T2 hypointense medial orbital mass (*black arrow*) displacing the right globe laterally (*white arrow*). Coronal T1-W post-contrast image (**c**) demonstrates peripheral nodular rim enhancement (*white arrow*) with intracranial extension and meningeal reaction (*black arrow*)

She subsequently underwent an incisional biopsy of the orbital tumor and histological examination revealed a proliferation of neoplastic CD-20 positive B-lymphocytes with extensive geographical and angiocentric necrosis. Epstein-Barr virus was positive in the lesional cells and there was an associated polymorphous infiltrate (Fig. 2). These features are consistent with a diagnosis of Grade 3 lymphomatoid granulomatosis.

She was then commenced on chemotherapy as for a diffuse large B cell lymphoma and had a good clinical response. Repeat MRI was performed after four blocks, which showed improvement; however, it was decided to change her treatment from conventional chemotherapy to treatment with rituximab.

For induction, she received two doses of rituximab 1 week apart from each other. MRI after these two doses showed residual tumor but significant interval improvement (Fig. 3).

She went on to receive four more doses of rituximab at 3-weekly intervals after which a repeat MRI revealed almost complete resolution of the tumor.

Based on her excellent clinical and radiologic response, it was decided to complete a total of six doses of maintenance treatment with rituximab.

Discussion

Lymphomatoid granulomatosis is a multisystem disease associated with Epstein-Barr virus that combines a granulomatous inflammatory process with lymphoproliferative potential [4]. It usually manifests in the 4th–6th decades, although there are a few case reports of its occurrence in childhood and early adolescence [3–5]. The prognosis tends to be poor and

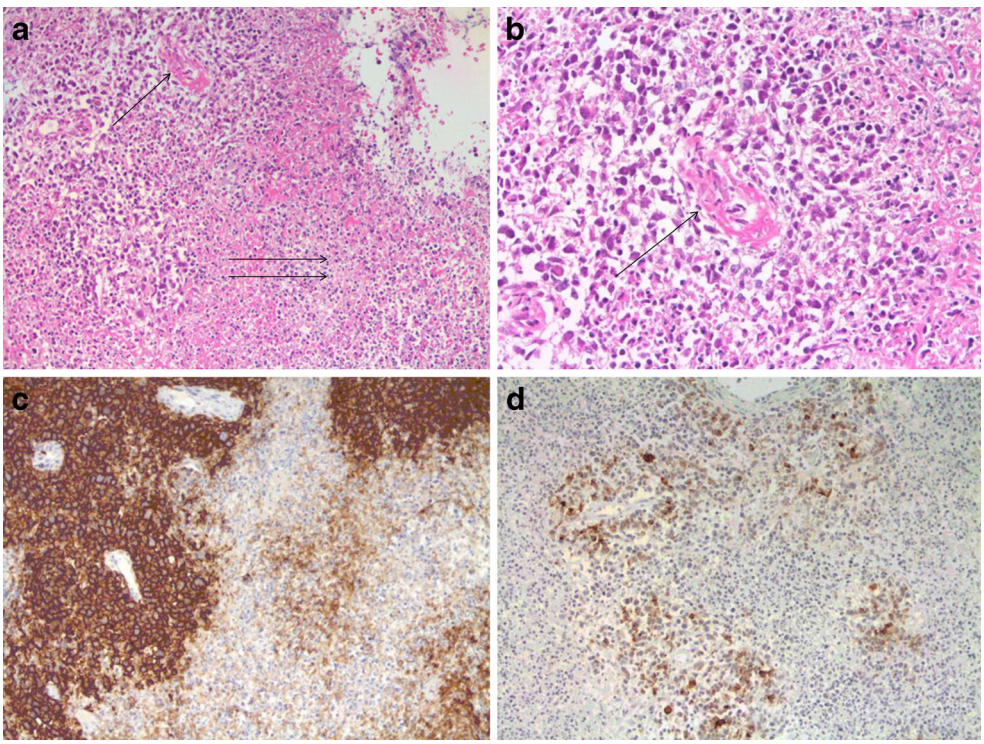

Fig. 2 Orbital tumor biopsy histology. Haematoxylin and eosin stain (**a**, **b**) shows an angiocentric infiltrate (*single arrow*) of large lymphoid cells in a background of smaller cells (**a** [100×], **b** [400×]). There is occlusion of the vessels with geographical necrosis (*double arrow*). The lymphoma cells are positive for the B-cell immunostain CD20 (**c** [100×]) and Epstein-Barr virus-latent membrane protein immunostain (**d** [100×]). These features are consistent with Grade 3 lymphomatoid granulomatosis

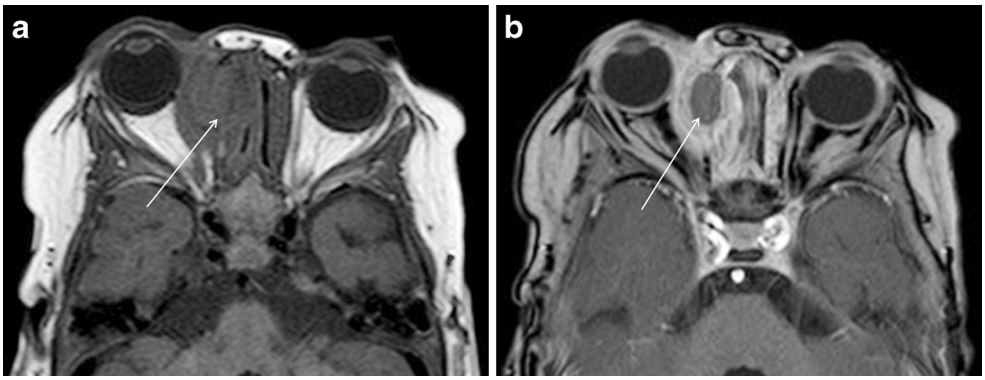

Fig. 3 Post-treatment follow-up MRI orbits 4 months later. Axial (**a**) and coronal (**b**) T1-W post-contrast images demonstrate interval improvement with a decrease in the size of the peripherally enhancing right orbital tumor (*arrows*)

mortality rates vary from 38% to 64% [3]. Lymphomatoid granulomatosis predominantly affects extranodal sites and multiple organ involvement is more common than single organ involvement in children [3]. The lungs are involved in more than 90% of cases at the time of diagnosis, with the chest radiograph typically showing a reticulonodular pattern [6], or multiple lung nodules of varying sizes [1, 5]. Central nervous system involvement has been described in 40% of cases, although ocular lymphomatoid granulomatosis is exceedingly rare [7]. Involvement of the skin, kidney, peripheral nervous system, spleen and liver have also been described in adults [2].

A single case of primary orbital lymphomatoid granulomatosis presenting as a mass has been described in a 54-year-old man; however, the orbital mass could not be seen in detail on MRI and the diagnosis was made after exploration and biopsy [7]. All other reported cases of orbital lymphomatoid granulomatosis found were confined to the globe and optic nerve in adults and ocular symptoms were preceded by pulmonary lymphomatoid granulomatosis [7].

MRI findings for central nervous system lymphomatoid granulomatosis have been reported. In contrast to our case, however, the multifocal round, globular or mass-like lesions are usually hyperintense on T2 [4, 8], in some cases with surrounding edema [3]. Ring-like, punctate or linear post-contrast enhancement has also been described and this is felt to be characteristic and related to the disease's effect on perivascular tissue and vascular walls [8]. We propose that the T2 hypointensity seen in our patient represents the highly cellular nature of the Grade 3 tumor, also the necrotising nature with similar imaging findings seen in Burkitt lymphoma and other granulomatous diseases such as tuberculosis and sarcoidosis.

In view of the high incidence of central nervous system involvement (51% of cases), it has been suggested that a brain MRI be considered in all children with lymphomatoid granulomatosis [3].

Lymphomatoid granulomatosis and post-transplant lymphoproliferative disorder are similar, yet distinct entities [6]. Although their exact relationship has not yet been established, they clearly differ in their immune response, with the former being T-cell rich, and the latter T-cell poor [6].

Lymphomatoid granulomatosis, like post-transplant lymphoproliferative disorder, is Epstein-Barr virus driven and patients may have an underlying immunodeficiency, hereditary or acquired. In a systematic review of 49 pediatric cases of lymphomatoid granulomatosis, approximately a third of the patients were immune compromised, either by an underlying immunodeficiency, or by therapy for another illness such as leukemia [3].

Histological diagnosis is required in view of the difficulty distinguishing the clinical features of lymphomatoid granulomatosis from granulomatous inflammation and other tumors. Lesions are characterised by an angiocentric, angiodestructive proliferation of atypical lymphocytes, with varying degrees of necrosis [1, 2]. In the current World Health Organization classification, lymphomatoid granulomatosis is grouped amongst the non–Hodgkin lymphomas as a neoplasm of mature B cells. The classification separates grades of lymphomatoid granulomatosis according to the proportion of large B cells, and the number that are positive for Epstein-Barr virus (Grades 1–3) [1, 2, 4]. All grades have the potential to evolve into aggressive lymphoma and the distinction between high-grade lymphomatoid granulomatosis and diffuse large B-cell lymphoma can be subtle [1].

Treatment has variable success and includes corticosteroids, anti–CD20 monoclonal antibodies such as rituximab, interferon and combination chemotherapy. Grade 1 and Grade 2 are responsive to interferon-alpha, while Grade 3 requires aggressive chemotherapy similar to diffuse large B-cell lymphoma. Radiotherapy has been considered in central nervous system disease although there is a high rate of relapse and progression to aggressive lymphoma [1, 2, 4]. A young age at diagnosis is also considered a bad prognostic factor [4].

In comparison, post-transplant lymphoproliferative disorder shows a polymorphic or monomorphic proliferation of plasma cells and lymphocytes, the earlier polymorphic lesion tending to regress with a reduction in immunosuppression while the monomorphic lesion or lymphomas require chemotherapy.

Our case constitutes a unique example of this rare lymphoproliferative disorder, as well as one of the first published cases of primary orbital lymphomatoid granulomatosis in a child.

Conflicts of interest None

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