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TEST YOURSELF: ANSWER

Test Yourself Answer to Question: A 31-year-old male presenting with a 1-year history of a non-tender lump over the thoracolumbar spine

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Answer: Extra-nodal Rosai Dorfman Disease (RDD).

Discussion

Ultrasound (Fig. 1a, b) demonstrated a lobulated hypoechoic mass within the subcutaneous fat and modest intralesional vascularity. MRI (Fig. 2a–c) demonstrated a well-defined lobulated mass returning isointense signal on T1W images, high signal on PDW FS images, and moderately high signal on T2W images when compared to skeletal muscle. The lesion was biopsied and histology (Fig. 3a, b) demonstrated a lesion composed of histiocytic cells featuring voluminous eosinophilic cytoplasm with a background of lymphocytes, plasma cells, and neutrophils. There were occasional histiocytes containing lymphocytes, in keeping with 'emperipolesis'. The large histiocytic cells were strongly positive on S100 immunohistochemistry (both nuclear and cytoplasmic). The features were consistent with a diagnosis of extra-nodal Rosai-Dorfman Disease (RDD).

Rosai-Dorfman Disease (RDD) is a non-Langerhans cell histiocytosis originally described in 1965 as 'sinus histiocytosis with massive lymphadenopathy' [1] and further described by Rosai and Dorfman in 1969 [2]. RDD primarily presents as the classical nodal form with bilateral cervical lymphadenopathy in children and young adults (mean age 20.6 years), resolving spontaneously in 20–40% [3, 4]. Extra-nodal disease occurs in ~ 40% of cases, occasionally occurring in the absence of nodal involvement and usually affecting older patients [4, 5]. Extra-nodal RDD typically involves the skin, subcutaneous tissues, nasal cavity, bone, and orbits [4, 6–8]. Cutaneous involvement occurs in 10% of patients with RDD whilst 3% have disease detectable only in the skin [9].

Subcutaneous involvement in RDD occurs in 9% of patients and may extend to the skin surface, presenting as a cutaneous mass [3]. Subcutaneous masses may be single or multiple and can be painful and rapidly growing [3, 8]. Commonly affected sites are the lower extremity, upper extremity, torso, and head and neck [3, 5]. Lesions may be infiltrative and muscle invasion can occur [3].

The underlying cause of RDD is not well understood but both sporadic and familial forms of the disease exist [4]. Recently clonality has been implicated, with Kinas mutations including ARAF, NRAS, KRAS, and MAP2K1 described [4]. Viral agents such as Epstein-Barr virus and herpesvirus 6 have a suggested link but this is yet to be proven [3, 4].

Nodal and extra-nodal disease appear histologically similar with emperipolesis (lymphocytophagocytosis) being the hallmark feature on a background of plasma cell-rich inflammatory infiltrate [3, 4, 10]. Neutrophils may be present but eosinophils are usually absent [4]. Histiocytes are positive for CD14, CD68, and S100 which stains both the nucleus and the cytoplasm. CD1a is consistently negative [10, 11]. Storiform fibrosis and IgG4-plasma cells may be present and result in pathological crossover with IgG4-related disease, which may also share some clinical features. As such, suspected cases of RDD should have serum IgG4 levels assessed [4].

MRI is the imaging modality of choice; lesions are typically hypointense or isointense on T1-weighted images and isointense to hyperintense on T2-weighted images when compared to skeletal muscle with restricted diffusion and

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homogenous contrast enhancement [3, 8]. FDG PET/CT demonstrates avid tracer uptake at sites of involvement [3, 8]. Subcutaneous lesions are typically hypoechoic on ultrasound and increased Doppler vascularity may be observed [3, 11].

The primary differential diagnosis of RDD is Langerhans cell histiocytosis (LCH) which can be excluded by negative staining for CD1a as well as an absence of eosinophils and emperipolesis [3, 4]. Newer stains such as Langerin (CD207) and mutation V600E of BRAF can also be used to identify cases of LCH [12]. S100 positivity is seen in both conditions [4]. Erdheim Chester disease (EDC) is another non-Langerhans histiocytosis but is negative for S100 and only involves the subcutaneous tissues in very rare cases [10]. Nodular fasciitis may appear similar on imaging, as can haematological malignancy and soft tissue sarcoma in cases of lymphadenopathy and subcutaneous soft tissue masses, respectively, but these differentials will be easily differentiated on histology [3]. There are imaging and histological similarities between cutaneous RDD and IgG4-related disease with abundant plasma cells and stromal fibrosis, a common histological finding shared by both disease [13]. High levels of IgG4-positive cells identified in some RDD lesions with the suggestion that the two diseases may lie on a spectrum [13–15].

Treatment of RDD depends on disease severity but may include observation, surgical excision, or systemic therapy with corticosteroids, tacrolimus, chemotherapy, or immunomodulatory therapy [4, 5, 8]. The role of radiotherapy is not established [5, 8]. Lesions may resolve spontaneously with conservative treatment, particularly nodal disease [3, 5]. Up to 10% of patients die from direct complications of the disease such as infection or amyloidosis [4], although mortality of up to 40% is seen in cases of extra-nodal RDD [3].

Declarations

Conflict of interest The authors declare no competing interests.

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