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Case Report

Dural involvement in central nervous system langerhans cells histiocytosis (LCH) on FDG PET/CT: Case report and review of CNS manifestations of LCH on PET/CT ☆

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ABSTRACT

We report a case of multisystem Langerhans cell histiocytosis in a pediatric patient with central nervous system involvement, highlighting F-18(FDG) uptake characteristics of dural sites of disease. We also highlight the advantages of functional data offered by FDG-PET as a useful follow-up tool to assess viability and, therefore, treatment response of previously known central nervous system lesions. The utility of recognizing characteristic patterns of FDG uptake in dural disease is also applicable in cases of diagnostic uncertainty, such as when evaluating isolated dural lesions or when distinguishing between Langerhans cell histiocytosis and similar appearing lesions such as meningiomas.

Introduction

Langerhans cell histiocytosis (LCH) is a rare disorder predominantly found among pediatric populations; annual incidence is only 1-2 cases per million (/10^6) adults but estimates range from 4-5/10^6 in children below age 15 old and 9.9/10^6 per million below 1 year of age (95% CI 5.5 to 16.3) [1,2]. It is characterized by granulomatous lesions sprouting from the pathologic proliferation of Langerhans cells but may also contain lymphocytes (primarily T-cells) and are often associated with abundant eosinophils and macrophages. However, it has a heterogeneous spectrum of phenotypic expression with clinical outcomes ranging from spontaneous remission to rapidly progressive and potentially fatal disease [3–5]. Later stage sequelae may also include skeletal disfigurement and/or neurodegeneration [6]. Clinical prognoses and courses of treat-

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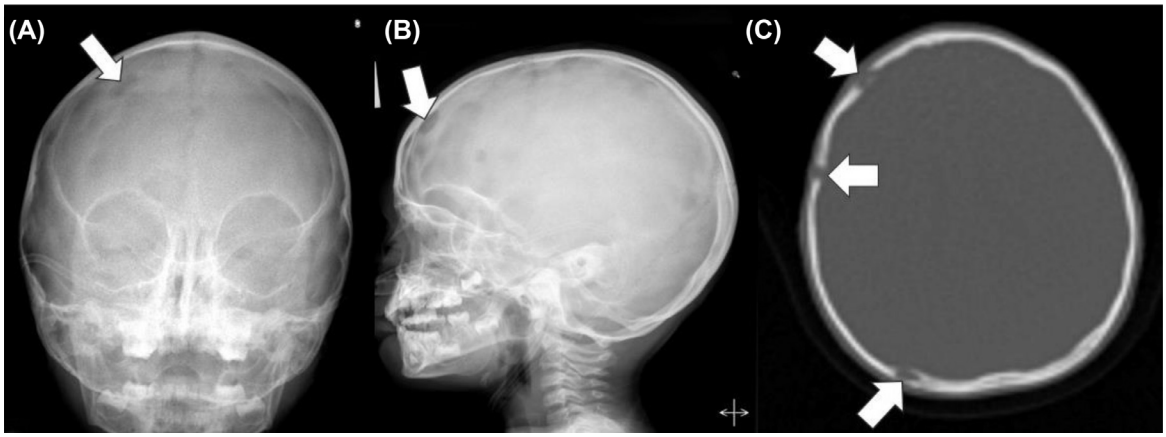

Fig. 1 – AP and lateral image views show a geographic skull with multiple punched out lytic lesions without sclerotic margins and A "bone within bone" appearance (A and B); axial CT shows multiple lytic lesions with "beveled edge" appearance (C).

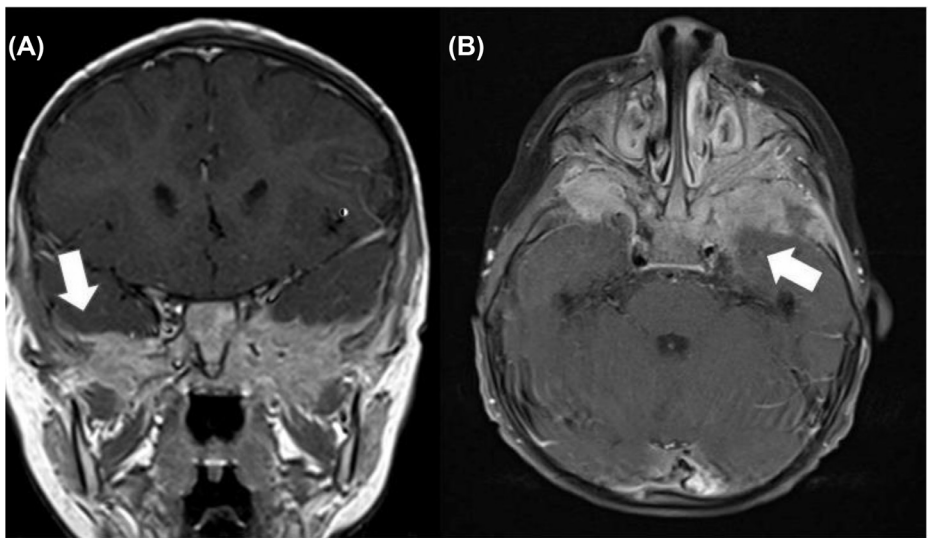

Fig. 2 – Coronal (A) and axial (B) contrast enhanced T1 weighted MRI (C) show extensive base of the skull involvement with enhancing soft tissue disease on MRI, predominantly involving the sphenoid wings.

ment vary with age as well as the extent and severity of disease [7].

Although most cases are limited to a single organ system, either at a single (unifocal) or multiple (multifocal) sites, they may potentially progress to multiple organ system (multisystem) disease [8–10]. Bones (80%) and skin (33%) are the most common organs [3,11]. CNS involvement is relatively rare (2%-4%); pituitary gland involvement (25%) is counted separately and manifests as diabetes insipidus [12,13]. However, its presence signifies increased risk of neurodegeneration, as do eye, ear, and craniofacial bone lesions; these are accordingly referred to as CNS risk lesions [3,14]. It should be noted that risk CNS lesions are considered indications for systemic therapy in pediatric cases. Nevertheless, there is currently insufficient published data to confirm whether this risk stratification also applies to adults receiving newly evolving targeted therapies [7].

In addition to detailed clinical assessment and laboratory panels, various imaging modalities such as magnetic resonance imaging (MRI), ultrasound, CT, X-ray, and bone scintigraphy are utilized both for initial staging of LCH and as well as treatment response assessment [3,15–18]. Certain imaging modalities offer diagnostic advantages when evaluating specific organ systems. For example, high resolution computed tomography (HR-CT; preferably with low dose multidetector system) is superior for assessing lung involvement; IV contrast is unnecessary as only cysts and nodules are typical of LCH.

Contrast enhanced MRI is superior for assessing intracranial cerebellar and extra-axial or dural lesions signifying CNS involvement, although case reports are infrequent [3,19,13,20,21]. However, despite the superior resolution and delineation of CNS morphology on MRI, it and other conventional imaging may still be diagnostically challenging,

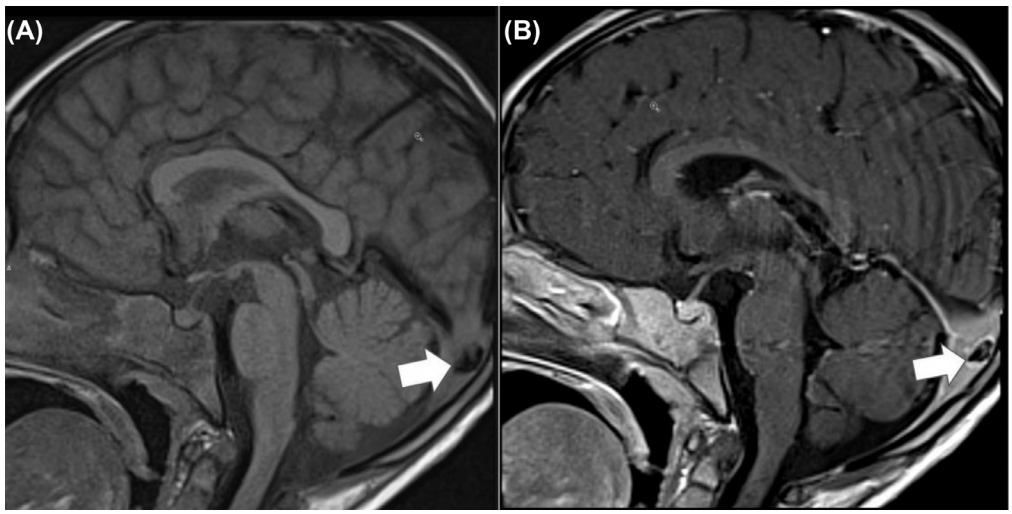

Fig. 3 – Sagittal T1-weighted sequences show an absence of a normal T1 intense neurohypophysis without infundibular thickening (A). Sagittal contrast enhanced T1 weighted MRI sequences show an isolated dural site of disease involvement at the level of the torcula (B).

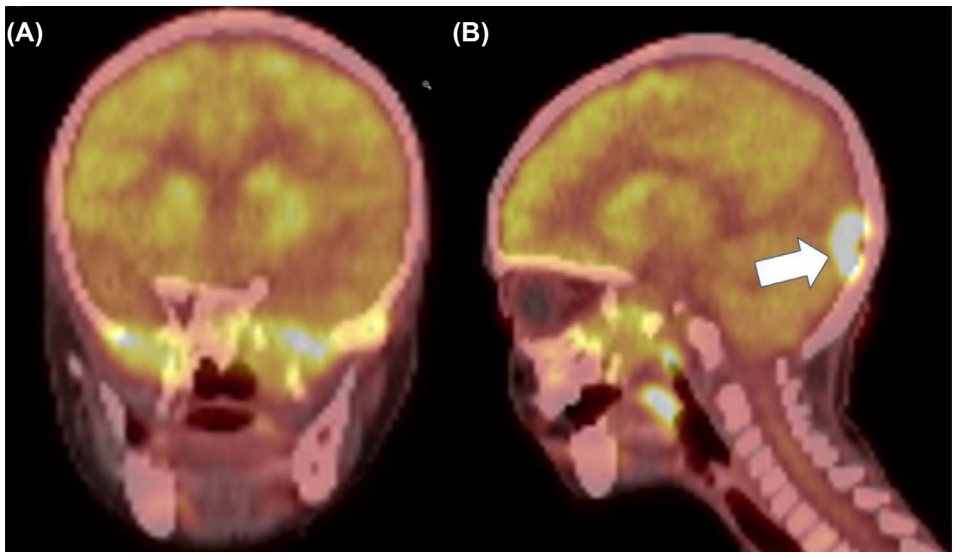

Fig. 4 – FDG-PET showing areas of intense uptake compared to background brain parenchyma corresponding to the base of the skull sites of involvement with disease (A). Similar extent of intensity of FDG uptake exhibited by the dural site of involvement with SUV-max measuring 11.4 (B).

especially when dural lesions and nonmass-like intra-axial disease exhibit imaging characteristics mimicked by other pathologies [22–25]. This is especially true with unifocal disease, which represents 40% of CNS involvement cases [26].

FDG-PET is uniquely suited for detecting glycolysis dependent histiocytic proliferation within LCH lesions and enables more accurate initial staging of intra- and extra-axial disease [14,19]. FDG avidity also serves as a metric for disease activity and post-treatment viability on follow-up imaging. Although distinguishing between inflammatory hyperplasia in reactive adenopathy and true nodal infiltration can be problematic, the rate of lymph node involvement is low (5%-10%) [19,27]. Furthermore, unlike other conventional imaging modalities, functional and anatomic FDG-PET data facilitates detection of systemic or whole-body disease, including high-risk multisystem disease, both during initial staging as well as subsequent therapy response assessment [19,25,28].

Case summary

Patient is a 2 year and 7-month-old previously healthy male who presented with polyuria, polydipsia, and weight loss. Additional signs included scalp rash and obtained labs were positive for central diabetes insipidus. LCH was clinically

suspected and subsequently confirmed with punch biopsy. Initial staging then included a panel of lab testing as well as imaging evaluation with a bone survey, US of the abdomen and retroperitoneum, brain MRI and whole-body PET-CT. Commensurate with the clinical picture, MRI revealed hypothalamic- pituitary axis involvement with absence of normal high signal intensity at the level of the neurohypophysis on T1 weighted sequences.

There was no thickening of the pituitary infundibulum nor post-contrast enhancement. Conventional imaging modalities also revealed calvarial and extensive skull base involvement (Fig. 1A-C), which was corroborated MRI findings which also demonstrated areas of dural involvement (Fig. 2A and B). Notable among extra axial CNS lesions was a focus of isolated dural thickening and contrast enhancement at the level of the torcula (Fig. 3A and B). The whole-body PET-CT likewise revealed the calvarial, skull base, and isolated dural lesions (Fig. 4A and B) plus additional extra-axial lesions as well as additional multisystem disease including multiple skeletal lesions, a solitary pulmonary lesion, and scattered subcutaneous nodules. All extra-CNS lesions exhibited similar FDG avidity greater than background brain parenchyma tissue (eg; isolated dural lesion at level of torcula showed SUV-max of 11.4).

Systemic chemotherapy was initiated for CNS involvement and multisystem disease, but the patient responded poorly with uncontrolled refractory disease after 3 cycles of clofarabine and daily trametinib. Follow-up PET-CT showed markedly intense uptake amid persistent dystrophic subcarinal mediastinal calcifications. A newly enlarged right perihilar node showing similar uptake was most concerning for disease proliferation. Granulomatous etiology was unlikely given the rapid interval development but was favored for a persistently stable calcified RLL lung nodule with low-grade uptake. Although the skull base disease markedly improved, residual disease was otherwise evidenced by small persistent foci of relatively increased uptake in the bilateral sphenoid bones and was the presumed etiology of persistently intense right occipital lobe uptake plus less conspicuous, although persistent focal uptake in the bilateral tibiae and femur. The patient was then readmitted for a fourth cycle of clofarabine and received pegfilgrastim upon discharge.

Discussion

We argue that our ability to discern characteristic FDG uptake patterns in dural based disease renders this PET/CT as a potentially useful adjunct to traditionally used conventional imaging for a more accurate initial staging of CNS disease, a vital step for directing disease treatment and predicting prognosis in this potentially lethal disease. Our argument stands particularly given evidence presented from literature that supports the utility of FDG positron emission tomography computed tomography (PET-CT) as an adjunct tool also for more accurate detection of intra-axial lesions, including nonmass-like disease, a particularly challenging entity to detect using conventional (ie; nonfunctional) imaging.

Functional and anatomic FDG PET-CT data is already recognized as playing a critical role in detecting systemic LCH lesions [19,29–31]. However, there is now growing evidence of its value as an adjunct tool to MRI and other conventional modalities for more accurate detection of CNS disease [32,33]. To our knowledge, this is the first case report highlighting the application of FDG-PET to identifying dural based LCH CNS involvement [34] and its potential to help differentiate similar appearing lesions depicted on conventional imaging [35].This would be particularly useful in cases of isolated dural or intra-axial LCH that can be diagnostically challenging, especially when the clinical picture is not clear-cut [32,33,36,37].

High on the list of differential diagnoses when evaluating dural lesions is meningioma, which can be a source of confusion and misdiagnosis in situations of isolated dural disease [38–42]. Although meningiomas are not conventionally evaluated with FDG-PET, literature shows that they are typically minimal-to-moderately FDG avid, depending on grade [43,44]. This is commensurate with the low metabolic activity expected in lesions whose overwhelming majority are low grade and slow growing [45]. Even in the absence of quantitative assessment, meningiomas at least typically show FDG uptake lower than background brain parenchymal tissue [45].

This functional data from measuring metabolic activity is what gives FDG-PET considerable advantage over conventional imaging as a metric for assessing LCH treatment response, especially at previously identified sites of CNS involvement.

Patient consent

Written informed consent for the publication of this case report was obtained from the patient.

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