Pediatr Radiol (2014) 44:234–238
DOI 10.1007/s00247-013-2786-y

CASE REPORT

Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease) with CNS involvement in a child

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Received: 13 May 2013 / Revised: 28 July 2013 / Accepted: 21 August 2013 / Published online: 5 October 2013

Abstract We describe the case of a 9-year-old boy with encephalitis associated with histiocytic necrotizing lymphadenitis (HNL), also known as Kikuchi-Fujimoto disease. The child presented with unilateral cervical lymphadenopathy and fever that evolved to encephalitis in 3 weeks. Brain MRI showed bilateral temporal lobe hyperintense signal on T2 and FLAIR, hyperintense FLAIR signal in the periaqueductal gray matter, medial walls of the third ventricle, and mammillary bodies, multiple diffusion restriction foci in a central perivascular distribution and central perivascular enhancement. The perivascular distribution and nodularity of the diffusion restriction seen in this case has not been previously reported in HNL encephalitis.

Keywords Histiocytic necrotizing lymphadenitis · Kikuchi-Fujimoto disease · Child · Magnetic resonance imaging · Computed tomography · Encephalitis

Introduction

Histiocytic necrotizing lymphadenitis (HNL), also known as Kikuchi-Fujimoto disease, is a rare form of lymphadenitis of unclear etiology and pathogenesis. The disease can mimic other causes of lymphadenitis such as lymphoma, cat scratch disease and tuberculosis [1–3]. Neurological complications occur in approximately 11% of the cases with a minority evolving to encephalitis [3–8]. We report a case of HNL encephalitis diagnosed in a 9-year-old boy, emphasizing the MR imaging features and pathological correlation. The MR imaging features of five previously published cases of HNL encephalitis are also reviewed [4–8].

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Case report

A 9-year-old boy presented to the emergency room with a 3-day history of fever and neck swelling for 10 days. C-reactive protein (CRP) was elevated (33.7 mg/L), white blood cell (WBC) count was low (3.6 × 106/dL), and hematocrit and hemoglobin were within normal limits (34.7 and 12.2 mg/dL). Past medical history was significant for sickle cell trait and asthma. Neck US showed left cervical lymphadenopathy and no abscess formation. The boy was treated with clindamycin IV for 4 days and ceftriaxone IV for 2 days. He was discharged home on oral amoxicillin-clavulanate for 7 days. Mononucleosis screen test, cytomegalovirus, Ebstein-Barr virus (EBV) and *Bartonella henselae* serology were negative.

Due to persistent high fever, night sweats and chills, the child was readmitted 9 days after discharge. Neck US showed stable left neck lymphadenopathy. Neutropenia and mild anemia persisted. The erythrocyte sedimentation rate was elevated (39 mm/h). Viral, mycobacterial and rheumatological serologies were negative. Computerized tomography (CT) confirmed left cervical lymphadenopathy in addition to minimal mucosal thickening of the maxillary sinuses and right mastoid air cells. Lymph node biopsy revealed a largely necrotic lymph node (Fig. 1) with extranodal extension of the

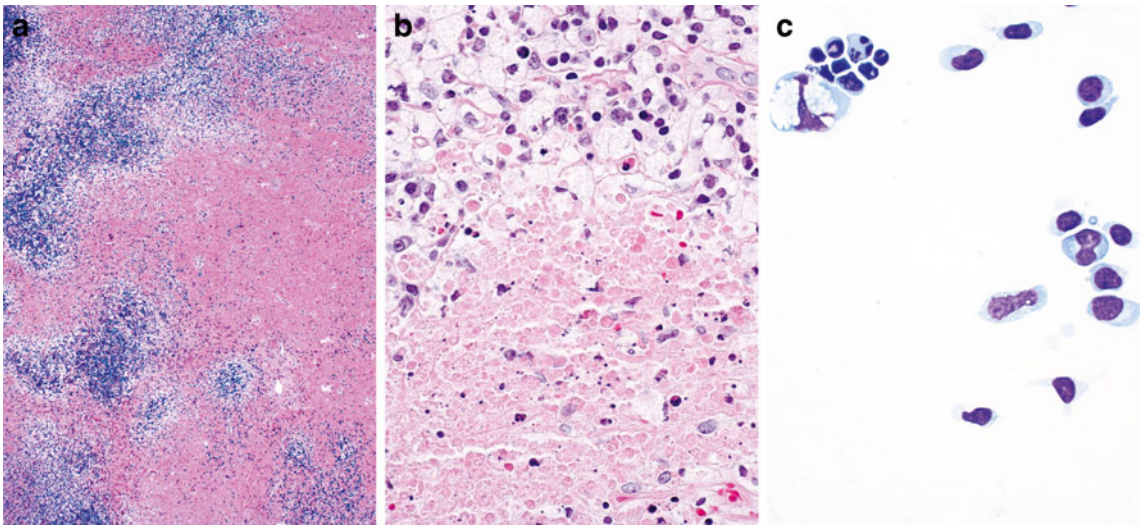

Fig. 1 Histopathology of left cervical lymphadenopathy (**a**, **b**) and cytopathology of CSF (**c**). **a** Low magnification of cervical biopsy shows predominantly necrotic lymph node with small islands of lymphocytes surrounded by foamy histiocytes (Hematoxilin-Eosin, original magnification x20). **b** High magnification demonstrates crescentic histiocytes (*upper*) surrounding areas of necrosis with frequent apoptotic figures without neutrophils (*lower*). Hematoxilin-Eosin, original magnification x400. **c** Cytospin preparation of CSF (Wright-Giemsa stain, original magnification x600) demonstrates high cellularity with multiple lymphocytes and monocytes (*right*) and occasional crescentic histiocytes surrounded by apoptotic figures (left upper corner)

necroinflammatory process. Immunohistochemistry showed residual parafollicular areas containing a mixture of CD20+ B- and CD3 + T cells with scattered large and somewhat atypical CD30 + /CD15- immunoblasts. CD8+ T cells dominated over CD4 + T cells by both immunohistochemistry and flow cytometry. A rim of CD68+ cells with eccentric nuclei (crescentic histiocytes) was present at the interface of the viable nodal tissue and necrotic zones (Fig. 1). These cells showed immunoreactivity with myeloperoxidase and lysozyme and were negative for CD56. Karyorrhexis without neutrophils was observed in the necrotic areas. Special stains were negative for fungal, bacterial or mycobacterial organisms. EBV in situ-hybridization and toxoplasma immunohistochemical staining were negative. An extensive immunohistochemical panel did not support metastatic tumor. Negative rheumatology tests and lack of significant plasma cell infiltrate in biopsy tissue argued against lupus lymphadenitis. Molecular genetic testing performed on the biopsy material was negative for clonal immunoglobulin and T-cell receptor genes rearrangements by BIOMED-2 multiplex polymerase chain reaction (PCR) assay and, therefore, not supportive of non-Hodgkin lymphoma. Flow cytometry showed a significant necrotic component along with mature CD45/side scatter populations consisting of mature lymphocytes (92%) and a diffuse myeloid region (7%). The constellation of findings pointed toward a reactive process; however, the extent of necrosis precluded exclusion of lymphoma with confidence. The differential diagnosis included histiocytic necrotizing lymphadenitis (HNL), infection, lupus lymphadenitis, Hodgkin or non-Hodgkin lymphoma, and metastatic solid malignancy with necrosis. Follow-up and re-biopsy in case of persistent or worsening lymphadenopathy were recommended. The child's fever and overall status improved and he was discharged home on naproxen.

The boy was readmitted 3 days later due to altered mental status and continuing fever. Head CT was normal. EEG demonstrated normal sleep and arousal states. Magnetic resonance imaging (MRI) showed increased T2 and FLAIR signal in the mesial temporal lobes, periaqueductal region, lateral wall of the third ventricle and mammillary bodies (Fig. 2). Multiple punctate areas of diffusion restriction were noted in a central perivascular distribution (Fig. 3). Perivascular enhancement was noted on T1-weighted magnetization transfer images (Fig. 4). Three-dimensional time-of-flight MR angiography and two-dimensional time-of-flight MR venography were normal. The differential diagnosis included histiocytic or lymphoid infiltration such as in HNL or lymphoma, as well as other disease processes such as microabscesses, granulomatous diseases (e.g., sarcoidosis), vasculitis and multiple emboli. Fluorodeoxyglucose-positron emission tomography (FDG-PET) showed FDG-avid predominantly left cervical and supraclavicular lymphadenopathy and a few FDG-avid lymph nodes in the pelvis, abdomen and bilateral inguinal regions, favoring lymphoma. Lumbar puncture was performed and revealed an opening pressure >45 mm of water. The CSF was pleocytic with elevated protein (77 mg/dl), suspicious for lymphocytic meningitis/encephalitis. A rapid plasma reagin test returned negative, excluding syphilis. Cerebral spinal fluid (CSF) cryptococcal antigen and mycobacterial cultures were also negative. Flow cytometry analysis of the CSF showed mature mixed lymphocytic populations and a minor population of necrotic events that exhibited the presence of

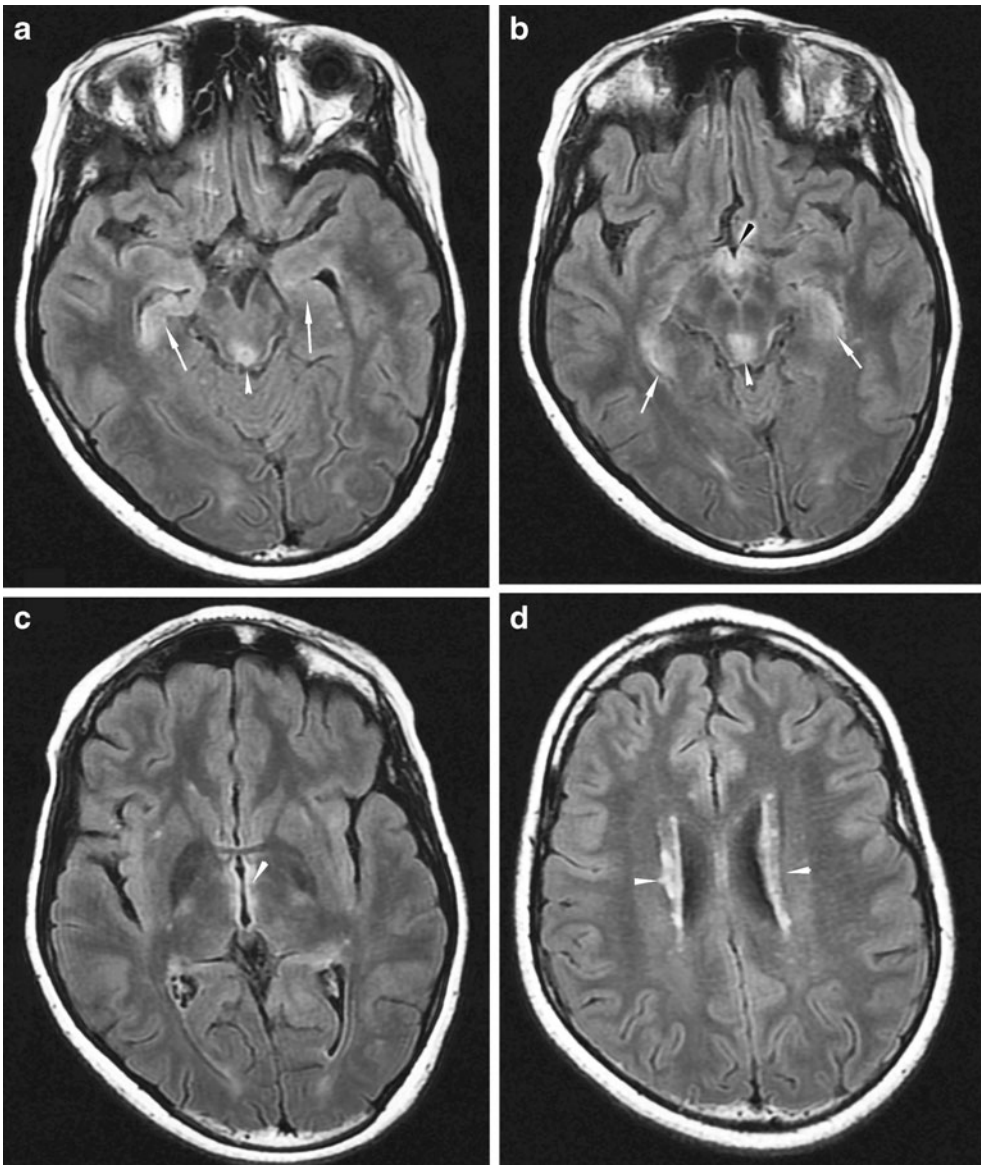

Fig. 2 Axial FLAIR image at the level of the suprasellar cistern (**a**) shows bilateral hyperintense signal in the mesial temporal lobes, more pronounced on the right (*arrows*). Hyperintense signal is also seen in the periaqueductal gray matter (*arrowhead*). Axial image through the midbrain (**b**) shows bilateral hyperintense signal in the hippocampi tail (*arrows*), periaqueductal gray matter (*white arrowhead*) and mammillary bodies (*black arrowhead*). Axial image at the level of the thalamus (**c**) shows hyperintense signal in the walls of the third ventricle (*arrowhead*). Axial image at the level of the lateral ventricles (**d**) shows bilateral hyperintense signal in the periventricular white matter (*arrowheads*)

T cells and monocytes. There was no indication of the presence of abnormal or clonal population to suggest malignancy. A second excisional biopsy was then performed yielding results identical to the first biopsy. Since malignancy, infection and lupus were excluded by the above-described work-up, the diagnosis of HNL (Kikuchi-Fujimoto disease) was rendered.

During hospitalization, the boy developed worsening somnolence, confusion and difficulty to ambulate and was given dexamethasone 10 mg/m_2/kg IV divided every 6 h for 10 days. Also, as the MRI had findings similar to Wernicke encephalopathy and the child had a history of poor nutrition, he was empirically started on thiamine 100 mg IV daily for 10 days. Thiamine status, however, was not biologically assessed. Six days after the third admission, the boy's mental status began to improve. A repeat MRI showed resolution of the diffusion restriction foci. The focal T2 and FLAIR signal abnormality in the periaqueductal gray matter and mesial temporal lobes also improved. The ventricles were prominent, likely as a consequence of steroid treatment. Subtle leptomeningeal enhancement was still noticed in the basilar cistern. Two weeks after the third admission, the child had significant clinical improvement, including mental status and ambulation, and was discharged on oral prednisone. Three-month follow-up showed continued improvement although some neurocognitive, neuropsychiatric and behavioral sequelae persisted.

Discussion

Histiocytic necrotizing lymphadenitis (HNL), also known as Kikuchi-Fujimoto disease, is a rare form of lymphadenitis of

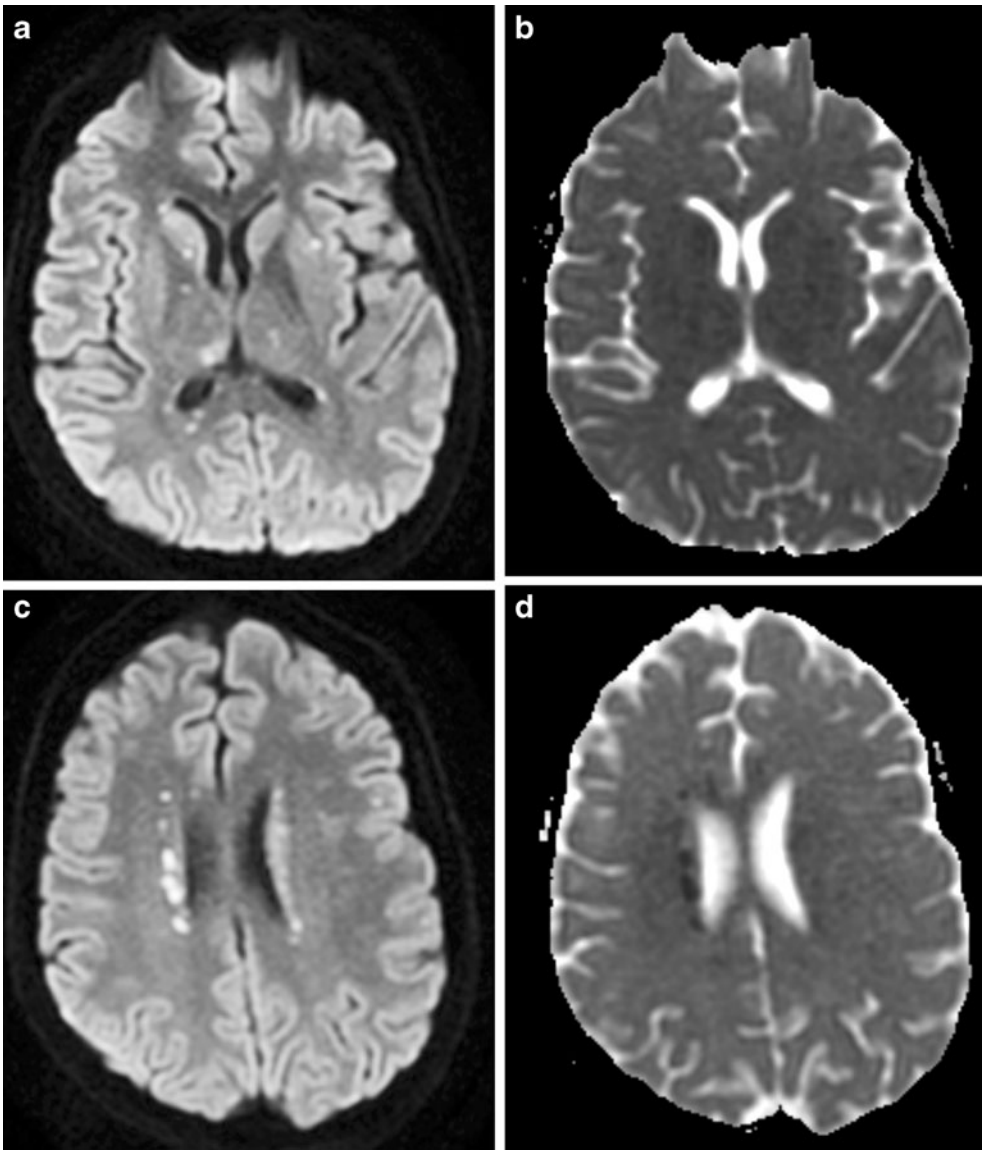

Fig. 3 Axial diffusion-weighted images and corresponding apparent diffusion coefficient maps at the level of the thalamus and basal ganglia (**a** and **b**) and superior aspect of the lateral ventricles (**c** and **d**) show multiple bilateral foci of diffusion restriction in a perivascular distribution

unclear etiology and pathogenesis described independently by Kikuchi and Fujimoto in 1972 [1, 2]. HNL has been proposed to represent a hyperimmune reaction of the monocyte-macrophage lineage to viral insults. A possible association between HNL and autoimmune disorders has also been noted, including systemic lupus erythematosus, mixed connective tissue disease, antiphospholipid antibody syndrome and scleroderma. HNL commonly presents as tender and painful cervical lymphadenopathy, usually involving the posterior cervical and jugular carotid chains. Bilaterality is seen in 30% to 50% of pediatric patients. Additional nonspecific signs and symptoms include prolonged low-grade fever, upper respiratory symptoms, malaise, arthralgia, myalgia, nausea, vomiting, fatigue, hepatomegaly, splenomegaly, parotid gland enlargement, interstitial lung disease and diarrhea. Weight loss and night sweats are rare. Skin lesions involving the face or upper body have been reported and are characterized by erythematous macules, papules, plaques, nodules and ulcers [3]. Laboratory tests are not specific and may include elevated CRP and erythrocyte sedimentation rate, leukopenia (<4,000 WBC/mm3) and atypical lymphocytes in peripheral blood. Necrotic lymph nodes are seen in one-third of the cases [3]. The differential diagnosis of HNL includes: 1) lymphoid malignancies, particularly non-Hodgkin lymphoma; 2) lymphadenopathy due to autoimmune disorders, primarily systemic lupus erithematosus; and 3) infectious etiologies such as EBV, herpes simplex virus (HSV), human herpes virus-6 (HHV-6), *Bartonella henselae* and toxoplasmosis. These diseases must be excluded before a final diagnosis of HNL is made.

HNL is self-limited with a 3–4% recurrence rate. There is no specific treatment although corticosteroids have been used in relapsing disease. The mortality rate has been estimated as approximately 2% [3]. The incidence of neurological

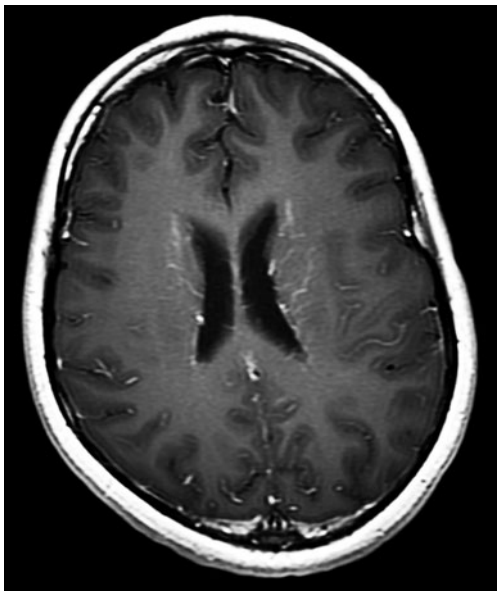

Fig. 4 Axial gadolinium-enhanced T1-weighted magnetization transfer image of the brain at the level of the body of the lateral ventricles shows bilateral linear enhancement in a central perivascular distribution

complications is estimated as approximately 11% based on a review of 244 cases. These include aseptic meningitis, mononeuritis multiplex, hemiparesis, brachial neuritis and photophobia. Aseptic meningitis has been reported in 2.8% to 9.8% of the cases and, therefore, the association with HNL is thought not to be coincidental.

Encephalitis with documented imaging features has been previously reported in 5 patients [4–8]. All were adult women with ages ranging from 19 to 39 years old. Four had cervical lymphadenitis and one had axillary lymphadenitis. The most common associated sign was fever (4/5), with night sweats, odynophagia, malaise, vomiting, diarrhea, arthralgia and ophthalmic vasculitis reported in isolated cases. Leukopenia was present in all patients with reported WBC count. Neurological signs and symptoms included altered mental status in all patients (loss of consciousness, disorientation, memory loss and drowsiness), with headaches and seizures seen in 3 of 5 patients. Most patients had remission of the signs and symptoms between 1 month and 14 months after initial presentation. MRI was performed in 4 of the 5 patients. Imaging features included: hyperintense T2 and FLAIR signal in the temporal lobes (3/4), pons (3/4) and basal ganglia (2/4) as well as midbrain, internal capsule and superior cerebellar peduncles occasionally seen. Ventriculomegaly was present in one patient [4]. Perivascular enhancement was seen in one case [8]. CT was normal in one of the patients who did not have MRI [5] with subtle hypodensity in the temporal region seen in another [6].

Besides increased T2 and FLAIR signal in the temporal lobes previously reported in HNL encephalitis [4–8], the current case had unique features, such as increased T2 and FLAIR signal in the walls of the third ventricle, aqueduct and mammillary bodies, resembling Wernicke encephalitis, as well as punctate foci of restricted diffusion along central perivascular spaces. The imaging features seen in this case as well as those described in prior case reports overlap with those of limbic, HSV and HHV-6 encephalitis, with additional features that may be seen in lymphoma and CNS tuberculosis.

As the present case illustrates, a precise diagnosis of HNL is challenging since features overlap those of non-Hodgkin lymphoma and also of reactive lymphadenopathy. The diagnosis is made by excisional biopsy of affected lymph nodes, as cytologic evaluation of fine needle aspiration material, even with the availability of flow-cytometric analysis or other ancillary studies, is insufficient to establish the diagnosis with confidence.

Conflicts of interest None.

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