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Localized Crystal-Storing Histiocytosis of the Posterior Fossa

Margaret E. Flanagan¹, C. Dirk Keene¹, David N. Louis², and Gordana Juric-Sekhar¹

¹Department of Pathology, University of Washington, Seattle, WA, USA

²Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Abstract

Crystal-storing histiocytosis (CSH) is an uncommon histiocytic proliferation reported to involve diverse organs and tissues, but involvement of the central nervous system (CNS) is rare. In most cases CSH is identified in association with underlying lymphoproliferative, plasma cell disease or rarely with various inflammatory or infectious conditions. CSH is characterized by the cytoplasmic accumulation of crystalline material in histiocytes, most commonly of kappa immunoglobulin light chain. We report a unique case of localized CSH involving the left cerebellum and caudal brain stem in a young man with a history of gout but without known lymphoproliferative or plasma cell disorders. Awareness of this entity is important diagnostically, but also to ensure appropriate management and follow-up, particularly in the absence of apparent underlying malignancy.

Keywords

central nervous system; crystal-storing histiocytosis; lymphoplasmacytic neoplasm; intracellular crystals; electron microscopy

INTRODUCTION

Crystal-storing histiocytosis (CSH) is an uncommon disorder and presents a diagnostic challenge for pathologists unfamiliar with the entity. It is characterized by an accumulation of almost exclusively kappa light chain aggregated into crystals in histiocytes.^{1,2,3} In most patients, CSH is a manifestation of an underlying lymphoplasmacytic disease, such as plasma cell dyscrasia, multiple myeloma or B-cell lymphoma.^{1,3,4} However, CSH can rarely occur in association with inflammatory process, such as multiple sclerosis or infectious conditions.^{1,5,6,7} CSH has also been reported in association with clofazimine treatment in the setting of lepromatous leprosy⁸, Charcot-Leyden crystal⁹ and hereditary cystinosis¹⁰, and asbestos exposure.¹¹ CSH can localize to a single site or can occur in a generalized form involving multiple tissue/organs. It affects a wide range of anatomic locations, such as lung, pleura, kidney, various sites in the head and neck, lymph nodes, bone marrow,

Correspondence to: Gordana Juric-Sekhar.

Correspondence: Gordana Juric-Sekhar, MD, PhD, Department of Pathology, Division of Neuropathology, 325 Ninth Avenue, Box 359791, Seattle, WA 98104, USA, gordana@uw.edu.

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gastrointestinal tract, breast, eye, orbit, skin, and heart.^{1,12} CSH involvement of the central nervous system (CNS-CSH) is rare.^{5,7,13–17} Here, we describe the first case of CNS-CSH involving the caudal brain stem and cerebellum. We also review the CNS-CSH literature to highlight the significance of this rare but important entity.

CLINICAL SUMMARY

A 36-year-old man presented with a 3-week history of progressive vertigo, headaches, diplopia and altered mental status with intermittent episodes of confusion, disorientation and difficulties with concentration. His past medical history included gout, hypertension, hyperlipidemia, traumatic brain injury, peripheral neuropathy of unclear etiology, and obstructive sleep apnea.

An initial diagnostic work-up was conducted with magnetic resonance imaging (MRI) of the brain. Results demonstrated a $2.8 \times 2.3 \times 1.9$ cm contrast-enhancing lesion involving the left middle cerebellar peduncle and adjacent pons and pontomedullary junction (Fig. 1). Neuroradiologically, suspicion for an intrinsic neoplastic process was high and stereotactic biopsy was performed. The diagnosis of CSH was made based on evaluation of large “Gaucher-like” cells in conventionally stained hematoxylin and eosin (H&E) sections, particularly under high magnification, and confirmation by immunohistochemistry and electron microscopy.

Further studies were done to determine possible association of CSH with systemic disorders expressing monoclonal immunoglobulins. Flow cytometry of cerebrospinal fluid samples was negative for abnormal B or T lymphocytes or plasma cells, and concurrent cytologic examination was negative for malignant cells. Serum protein electrophoresis (SPEP) was unrevealing for underlying monoclonal gammopathy. Urine protein electrophoresis (UPEP) showed presence of protein bands, but immunofixation was negative. Peripheral blood flow cytometry and bone marrow biopsy were negative for a lymphoproliferative disorder. A CT scan of the chest, abdomen and pelvis, and a testicular ultrasound were negative for mass lesions or other relevant abnormalities. Because the patient’s complaint of diplopia, ophthalmological examination was performed and was normal. Studies for *Helicobacter pylori* were negative; this was done because of previously reported association between this bacterium and gastrointestinal CSH.

The post-operative course was complicated by a surgical wound infection, which was treated effectively with antibiotics. Approximately one-month post-biopsy, the patient developed a rash involving his entire body, which was considered secondary to antibiotic use, and for what the patient received a 6-day course of methylprednisolone with improvement of his symptoms. Skin biopsies were negative for possible cutaneous involvement by CSH. The patient was neurologically intact. A follow-up MRI of the brain performed at three and four months later demonstrated complete spontaneous resolution of the enhancing lesion. After that, the patient was lost to follow up.

PATHOLOGICAL FINDINGS

Histopathological evaluation demonstrated brain parenchyma with predominantly mixed inflammation composed of CD3- and CD20-immunoreactive lymphocytes and rare CD138-positive plasma cells, primarily in a perivascular distribution. Most striking were “Gaucher-like” CD68-immunopositive cells in clusters or individually characterized by oval bland nuclei and abundant eosinophilic cytoplasm with layered PAS-negative intracytoplasmic fibrillary material. Electron microscopy from the paraffin-embedded material demonstrated an accumulation of elongated osmiophilic and needle-like crystalloid inclusions located in the cytoplasm of numerous histiocytes. In addition, these cells exhibited a strong kappa light chain predominance over lambda light chain by both immunohistochemistry and *in-situ* hybridization. The absence of immunoreactivity for IgG, IgA, IgD or IgM showed that immune deficiencies and monoclonal gammopathies were not present. The Epstein-Barr virus-encoded small RNA (EBER) *in-situ* hybridization to detect Epstein-Barr virus-driven processes, such as lymphoproliferative diseases, was negative. Flow cytometry studies of the brain parenchyma revealed a scant B-cell population with increased kappa-to-lambda ratio. Hematopathological consultation did not suggest a lymphoproliferative-plasmacytic disorder or neoplastic histiocytic process. BRAF V600E mutation was not detected in histiocytic cells by immunohistochemistry. The histopathologic features are highlighted in Figure 2.

DISCUSSION

CSH has been reported in various organs^{1,6,8,12}; but CNS-CSH is a distinctly rare disease with only six cases reported in the literature.^{5,7,13–17} These cases, and the case reported here, presented as mass lesions (Table 1), but this is the first case localized to posterior fossa structures, including the caudal portion of the brainstem and cerebellum. Interestingly, all reported CNS-CSH cases, including our patient, share an isolated restriction to the CNS, suggesting that CNS-CSH occurs independently from systemic multiorgan involvement, which primarily affects the bone marrow, lymphoreticular system and kidneys.¹ Cases of isolated CSH, which account for more than 50% of all cases, the head and neck, and the lung and pleura are the most frequent locations¹, but rare sites such as breast¹², bone¹⁹, and heart¹ have been reported. Although approximately 90% of all CSH cases occur in the setting of an underlying hematological diseases, the majority of CNS-CSH cases are associated with inflammatory conditions such as Crohn’s disease⁷, vasculitis¹⁷, or possible infection¹⁴, in addition to our patient, who has a history of gout. There has been a slight sex predilection in the CNS-CSH cases, many of which are reported in young women^{5,7,13,14,15,17}, with exceptions of this case of a young man and another case reported in a middle-aged man older than our patient.¹⁶

Diagnosis of CSH requires a careful evaluation of histiocytes in conventionally stained hematoxylin and eosin (H&E) sections, particularly under high magnification, and confirmation by immunohistochemistry and/or electron microscopy. Diagnosis can be missed when H&E stains are deeply eosinophilic and opaque, which can obscure the crystals or striations on microscopic examination.¹ CSH may also be easily confused with other types of histiocytoses, such as Erdheim-Chester or Rosai-Dorfman disease, or storage disorders such as Gaucher disease.³ Due to the cytomorphological similarities, crystal-

storing histiocytes have been called “pseudo-Gaucher cells”.² However, the cells in thalassemia and chronic myeloid leukemia share the same name; thus the term “pseudo-pseudo-Gaucher cells” has been proposed for the specific type of histiocytes in this entity.¹⁸ In addition, ultrastructural assessment via transmission electron microscopy is helpful since true Gaucher cells contain tubular structures, while crystal-storing histiocytes usually have membrane-bound cytoplasmic electron-dense rhomboid crystals.²

The crystals in CSH are consistently PAS negative, and are composed of a monoclonal immunoglobulin (Ig) light chain, generally of kappa type¹, as seen in our case. The specific pathogenesis of crystal formation remains unclear, but multiple factors may be involved. One hypothesis proposed that the abnormal amino acid sequences linked to monoclonal gammopathy possess a clone of plasma cells with specific immunoglobulin gene rearrangements, which promote abnormal crystallization, or that histiocytes have a defect in processing these abnormal immunoglobulins.^{1,15,19,20} Rare cases of CSH can be complicated by a variety of benign disorders associated with inflammatory background or hyperactivated immune system.^{1,5,6,8} In the absence of an identified lymphoproliferative or plasma cell disease, crystal-containing cells can represent a reaction to high values of normal immunoglobulins in the setting of inflammation^{6,21}, and crystallogenesis may be attributed to either overproduction or decreased clearance of immunoglobulins.^{2,3} These mechanisms may have been associated with isolated CNS-CSH without hematological disease.^{5,7,13,14,16,17} However, there is no known association between CHS and hyperuricemia, which was present in our patient.

It is debatable whether this disease is a neoplastic or a reactive process, as CSH can be the consequence of either a neoplastic or non-neoplastic condition. Cases with multiorgan involvement and recurrence after surgical excision of the lesion support the neoplastic nature of histiocytic proliferation.²² Also, the histiocytes represent a continuum in this condition where initially the cell start out as reactive and localized, and could possibly undergo neoplastic transformation¹⁹ as occurs in other chronic reactive conditions, such as ulcerative colitis. Our patient’s brain biopsy was associated with lymphoplasmacytic infiltrates, but this was insufficient to make a diagnosis of lymphoproliferative/plasma cell disease in the setting of scant predominantly perivascular mixed T- and B-lymphocytic populations and a negative laboratory workup. This disease can be considered a reactive process with the inflammatory cells potentially representing a response to tissue injury from the pathological process leading to accumulation of crystalline material.⁷ This assumption may be supported by the findings observed in a WHO grade I meningioma with prominent lymphoplasmacytic infiltrates associated with crystalline kappa predominant plasma cell inclusions without known history of plasma cell disease.²³

There is scant information available about specific response of CSH following chemotherapy or surgical treatment.¹ Given the limited clinical experience with CSH in the CNS, the optimal treatment and prognosis remain unclear, and in most of the cases, the treatment was dependent on the associated underlying condition. Only in one previous case with isolated CNS-CSH⁵ and in our patient, a course of steroids was given. The case reported by Constanzi et al⁵ met criteria for diagnosis of multiple sclerosis that was initially steroid responsive, but due to the atypical clinical features, rapid progression and persistent white

matter enhancement, a brain biopsy was performed, which revealed a clonal plasma cell proliferation in association with CSH. In our case, the patient was given steroids secondary to an allergic reaction to antibiotics with resolution of his symptoms and enhancing lesion in brain through MRI assessment. In three other CNS-CSH cases^{5,15,17} patients received treatment with positive response and stabilization of the disease. Interestingly, only our patient and a 38-year-old female patient¹⁷ had documented resolution of their lesions after treatment. Clinical implications of this diagnosis are not well understood, as reported clinical courses range from indolent without recurrence¹ to rapid progression.² Overall, patients with localized disease have a better prognosis than those with the generalized, multiorgan variant.¹ Clinical course appears to depend on the inherent biology of the associated neoplasm and/or severity of the underlying inflammatory process.¹⁹ Although the available data of CSH confined to the CNS, and as in our case, suggests that the disease may be relatively indolent and can be controlled with treatment. Since the vast majority of reported CSH cases are associated with an underlying lymphoproliferative or plasma cell neoplasm¹, we propose continued follow up for patients who present with this entity in the absence of an apparent underlying malignancy.

In conclusion, it is important to recognize CNS-CSH for accurate diagnosis and appropriate follow-up management, particularly in patients with previously unrecognized lymphoproliferative/plasma cell disorders.

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Fig.1.
MR images of the brain; sagittal (A) and axial (B) T1- weighted with gadolinium contrast images reveal a lesion involving the left cerebellar peduncle with adjacent brain stem

Fig.2.

Pathological findings of crystal-storing histiocytosis involvement of the central nervous system; mildly hypercellular brain parenchyma containing a mixed inflammatory infiltrate composed of lymphocytes, histiocytes and occasional plasma cells (A); “pseudo-Gaucher” histiocytes with bland oval shaped nuclei and abundant eosinophilic cytoplasm (B); “pseudo-Gaucher” histiocytes on higher magnification with intracytoplasmic fibrillary material (C) demonstrating CD68 immunoreactivity (D) and strong kappa light chain predominance on *in-situ* hybridization (E) and immunohistochemistry (F); electron micrograph demonstrating an accumulation of cytoplasmic elongated osmiophilic and needle-like crystalloid inclusions within histiocytes (G). (A-C: H&E, D: CD68, F: kappa light chain immunohistochemistry; E: kappa light chain *in-situ* hybridization; Scale bars: A,B: 80 μ m, C-E: 40 μ m, F: 60 μ m, G: 980 nm)

Table 1

Clinico-pathological characteristics of cases with crystal-storing histiocytosis of the central nervous system

Case	Age/ Gender	Symptoms prompting workup	Imaging (MRI)	Patient history/underlying disease	Bone marrow	Histiocytes (heavy/light chain)	Treatment	Outcome, follow-up (duration)
Constanzi <i>et al.</i> (5) Rodríguez <i>et al.</i> (13)	32/F	Right sided visual blurring; headaches; right-sided weakness; aphasia; confusion	Multiple contrast enhancing mostly white matter lesions in the brain and spinal cord	NE; Some plasma cells with plasmablastic features identified in repeated brain biopsy 3 years after initial diagnosis	Normal	NA/Kappa	Dexamethasone; Mycophenolate; Melphalan; Lenalidomide; Brain radiotherapy	Alive, progression within 3 years after initial diagnosis; stabilized (for ~24 months)
Johnson <i>et al.</i> (14)	20/F	Headaches; sore throat	3.5 cm contrast enhancing lesion of the left temporal lobe	Possible prior infection	NA	Lambda	NA	NA
Kaminsky <i>et al.</i> (7)	27/F	Left-sided tremor and tingly sensation; numbness	6.1 cm contrast enhancing irregular lesion of the right parietal lobe	Crohn’ s disease	NA	NA	NA	NA
Orr <i>et al.</i> (15)	38/F	Tonic-clonic seizure	Contrast enhancing lesion of the right parietal lobe	Plasma cell proliferation	Normal	IgA/kappa	Brain radiotherapy; Rituximab	Alive, stabilized (for 17 months)
Woehrer & Kovacs (16)	56/M	NA	NA	No disease	NA	NA	NA	NA
Prezeshkpour <i>et al.</i> (17)	38/F	Seizures	Bilateral frontal lobe	Intracerebral angitis	Normal	Polyclonal Ig	Cyclophosphamide	Resolution of lesion
Current case	36/M	Vertigo; headaches; diplopia; confusion; disorientation; concentration difficulties	2.8 cm contrast-enhancing lesion of the left middle cerebellar peduncle and adjacent pons	Gout	Normal	Kappa	Methylprednisone	Alive, resolution of the lesion on MRI (for 3 months)

F, female; M, male; MRI, magnetic resonance image; NA, data not available; NE, not established