

BRIEF REPORT

**Juvenile xanthogranuloma manifesting with LCH-associated neurodegenerative
disease-like radiological findings**

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23 **Abbreviations:**

CNS	Central nervous system
CT	Computed tomography
ECD	Erdheim–Chester disease
ERK	Extracellular signal-regulated kinase
FFPE	Formalin-fixed paraffin-embedded
FLAIR	Fluid attenuated inversion recovery
IVIG	Intravenous immunoglobulin
JLSG	Japan Langerhans Cell Histiocytosis Study Group
JXG	Juvenile xanthogranuloma
LCH	Langerhans cell histiocytosis
MAPK	Mitogen-activated protein kinase
MRI	Magnetic resonance imaging
ND	Neurodegenerative disease
RDD	Rosai–Dorfman disease

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ABSTRACT

Here, we describe two patients with juvenile xanthogranuloma (JXG) manifesting with Langerhans cell histiocytosis-associated neurodegenerative disease (ND)-like radiological findings. One patient showed typical radiological abnormalities at onset, which worsened with progressing central nervous system symptoms 7 years after LCH-oriented chemotherapy. Another showed spontaneous regression of clinical symptoms, with a transient radiological change 1 year after salvage chemotherapy for recurrence of JXG. These data regarding JXG-associated ND will facilitate future investigation of the disease, as well as development of therapeutic interventions.

1 | INTRODUCTION

Juvenile xanthogranuloma (JXG), the most common form of non-Langerhans cell histiocytosis (LCH), is thought to arise from dermal dendrocytes or macrophages. The majority of patients with the disease present primarily with skin lesions, which usually regress spontaneously. However, some patients develop extracutaneous lesions, with or without cutaneous lesions (i.e., systemic JXG); sometimes, these lesions can progress rapidly and can reduce quality of life, or even become life-threatening, despite aggressive LCH-oriented chemotherapy.^{1,2} Similar to other histiocytic disorders such as LCH and Erdheim–Chester disease (ECD), patients with systemic JXG often harbor somatic mutations in the mitogen-activated protein kinase (MAPK) pathway genes, most notably BRAF.³

LCH affects the central nervous system, manifesting primarily as diabetes insipidus, or more rarely as neurodegenerative disease (ND). LCH-associated ND, characterized by progressive radiological abnormalities of the cerebellum, basal ganglia, and pons, as well as cerebellar dysfunction accompanied by cognitive impairment and behavioral disturbance, can develop many years after treatment for LCH.⁴ Involvement of multiple organ systems, particularly the pituitary gland, skin, base skull, or orbit bone involvement, and presence of the BRAF V600E mutation, are risk factors for developing LCH-associated ND.⁵

ND also occurs in patients with ECD;⁴ however, there is no report about ND in patients with JXG. Here, we report two cases of JXG who presented with radiological abnormalities similar to those observed for LCH-associated ND.

2 | CASE REPORT

(Case 1) A 7-year-old boy, who developed diffuse papules on his trunk and extremities 1 year previously, was admitted to our hospital due to polydipsia and polyuria. Cranial magnetic resonance imaging (MRI) revealed swelling of the pituitary gland and multiple T2-hyperintense lesions in the cerebellum (Fig. 1A). Bone scintigraphy, and cervical and thoracoabdominal computed tomography (CT) showed no disease involvement associated with ECD. He had no long bone involvement or other classic radiographic findings associated with ECD. Histopathological examination of a papule resected from his waist revealed accumulation of skin dendrocyte-derived histiocytes, which were positive for CD68 and FXIII, and negative for S100, CD1a, CD207 (langerin), and BRAF V600E. Therefore, the patient was diagnosed with systemic JXG.

Although a 1-year LCH-oriented chemotherapy consisting of vincristine, cytarabine, prednisolone, methotrexate, 6-merkaptpurine, vindesine, according to the Japan Langerhans Cell Histiocytosis Study Group-02 (JLSG-02) protocol,⁶ resulted in long-term stabilization of the disease,⁷ his gait was unstable, and he developed ataxia and cognitive deterioration 7 years after treatment. Cranial MRI revealed widespread T2-hyperintense lesions in the bilateral cerebellar dentate nuclei, a finding similar to typical MRI findings in cases of LCH-associated ND (Fig. 1B). Despite monthly intravenous immunoglobulin (IVIG) therapy for approximately 3 years, his neurological symptoms worsened gradually. No genomic data were derived from old formalin-fixed paraffin-embedded (FFPE) samples due to the low amount of DNA that could be extracted.

(Case 2) A 1-year-old boy presented with fever, papules on his face, pancytopenia, and hepatosplenomegaly. Gallium scintigraphy and cervical and thoracoabdominal CT showed no long bone involvement or other classic radiographic associated with ECD. Cranial MRI revealed no abnormal findings. Histopathological examination of a papule and liver biopsy revealed proliferation of histiocytes, which were positive for CD68 and FXIII, and negative for S100, CD1a, CD207, and BRAF-V600E. He was diagnosed with systemic JXG.

The patient underwent a 1-year LCH-oriented chemotherapy, according to the JLSG-02 protocol,⁶ during which he achieved complete remission. Although he experienced relapse of the skin and bone marrow 1 year after the initial treatment, salvage cladribine monotherapy led to second complete remission. One year after the salvage treatment, he complained of frequent falls, and fluid attenuated inversion recovery (FLAIR)

cranial MRI revealed bilateral hyperintense lesions in the cerebellar dentate nuclei (Fig. 2A). Both his neurological symptoms and radiological findings improved spontaneously (Fig. 2B). Droplet digital polymerase chain reaction and next generation sequence analyses of FFPE samples^{8,9} failed to detect the somatic mutations frequently found in histiocytic neoplasms, including BRAF, MAP2K1, KRAS, NRAS, CSF1R, and ALK.

3 | DISCUSSION

Despite recent advances in molecular diagnosis of histiocytic disorders, some issues remain unresolved regarding their association with ND, including pathophysiology and treatment. Although LCH, ECD, and systemic JXG have distinct clinical and pathologic features, these histiocytic disorders are categorized into the “Langerhans (L)” group, mainly because they harbor somatic mutations in the MAPK pathway, and LCH/ECD and LCH/JXG histological phenotypes can co-exist in a single case.^{3,10-12} The present two cases raise the possibility that patients with all disease types categorized in the L group can develop ND.

In the present cases, multiple organ systems were initially affected, which is considered to be a risk factor for developing LCH-associated ND.⁵ In case 1, abnormal MRI findings in the cerebellum, which were present already at onset, progressed gradually after chemotherapy, followed by development of cerebellar dysfunction and cognitive impairment. By contrast, the clinical symptoms and abnormal MRI findings in case 2 disappeared spontaneously. Such inter-patient heterogeneity has been reported for LCH-associated ND.¹³ Nonetheless, careful screening and long-term follow-up are required to detect development of ND in patients with systemic JCG.

Currently, there are two prevailing theories on the pathogenesis of LCH-associated ND. One hypothesis is that MAPK activation of embryonic erythro-myeloid progenitors, mostly by BRAF V600E mutation, leads to clonal expansion of tissue-derived macrophages (i.e., microglia in the CNS) and development of ND.¹⁴ Another is that a somatic BRAF V600E mutation in peripheral hematopoietic progenitors results in infiltration of mutated monocytes in the brain and development of ND.¹⁵ We speculate that a similar mechanism is involved in the development of JXG-associated ND, although we could not identify any mutations of the MAPK pathway in either case.

One of the greatest concerns is development of effective treatments for JXG-associated ND. Monthly IVIG treatment failed to improve the disease status of ND in case 1, as reported for cases of LCH-associated ND.^{13,16} One possible second-line therapy is cytarabine-containing chemotherapy, in combination with vincristine, dexamethasone, or IVIG, which has been effective for some patients with LCH-associated ND.^{13,17,18} Because a BRAF inhibitor may be a promising option for LCH-associated ND,¹⁹ discovery of clinically meaningful therapeutic targets is mandatory.

In conclusion, additional studies are required to obtain more data regarding JXG-associated ND, which will serve as a starting point for further investigations and development of drugs to treat histiocytic disorder-associated ND.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest associated with this manuscript.

FIGURE LEGENDS

Figure 1. T2-weighted Magnetic resonance imaging (MRI) findings in case 1 at onset (A) and at 7 years post-treatment (B). Arrows indicate hyperintense lesions in the cerebellum.

Figure 2. Fluid attenuated inversion recovery (FLAIR) MRI findings in case 2 at 1 year (A) and 3 years post-treatment (B). Arrows indicate hyperintense lesions in the cerebellum.

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