Observation of notable therapeutic response in a patient with systemic juvenile xanthogranuloma with KIF5B-ALK fusion

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Abstract

We report the case of a 1-year-old male patient with systemic juvenile xanthogranuloma in whom central nervous system lesions caused developmental retardation, spasticity and clonus of the lower extremities. He needed tube feeding and experienced severe bronchitis and generalised convulsive seizure. KIF5B-ALK fusion was identified in the cutaneous lesion, and he was administered alectinib, an ALK inhibitor. Two months after the initiation of alectinib administration, the central nervous system lesions achieved partial regression. The spasticity and clonus were also relieved. A high index of cognition is needed for ALK fusion in infants with histiocytosis.

Introduction

Juvenile xanthogranuloma (JXG) is classified as a histiocytosis that is generally diagnosed on the basis of the presence of cutaneous nodules in infancy. It has been considered benign and could undergo spontaneous regression without therapy.[1] However, some patients with systemic JXG, particularly patients with central nervous system (CNS) involvement, might have severe neurological sequelae.[2] Conventional chemotherapy based on Langerhans cell histiocytosis (LCH) have been applied for these severe cases,[2] but the response rate remains unclear. In addition, adverse events and late complications induced by anticancer drugs should be avoided in paediatric patients as much as possible, especially in neonates. Recently, BRAF V600E mutation and recurrent kinase fusions, including BRAF, NTRK and anaplastic lymphoma kinase (ALK), including KIF5B-ALK fusion, have been identified in histiocytic neoplasms.[3,4]. We present the case of a patient with systemic JXG with KIF5B-ALK fusion detected by next-generation sequencing (NGS) panel -based comprehensive genome profiling (CGP) for solid tumours, in whom CNS lesions had caused neurological disorders. There has been no report about ALK inhibitor for an infant case of histiocytosis.

CASE PRESENTATION

The patient was a 1-year-old male infant born to non-consanguineous Japanese parents. He presented with multiple subcutaneous tumours of up to 6.0 cm in diameter when he was 2 weeks old (Fig. 1A). No neurological abnormality was found except the lack of movement in his right arm. His laboratory test findings were within normal limits. An enhanced computed tomography (CT) scan demonstrated subpleural nodular shadows in both lung fields (Fig. 1B), and multiple low-density areas in the liver (Fig. 1C) and in the right kidney (Figure. 1D). Brain and whole spine magnetic resonance imaging (MRI) revealed enlargement

of the left side of the medulla, the tumour of cerebellum, and an intra-axial massive tumour with contrast enhancement in the cervico-thoracic spinal cord. Biopsy of a cutaneous lesion was performed, and spindle cells with circular unequal nucleus and light cytoplasm were proliferating between the dermal collagen fibres (Fig. 2A-C). Immunohistochemical staining showed that the cells were positive for CD68, CD4, factor XIIIa and CD163 but negative for CD1a, CD34, CD21, CD35, and s-100 protein. In addition, ALK D5F3 and ALK1 were positive (Fig. 2D-F). Taken together, the diagnosis of JXG was made.

The patient did not receive any anti-tumoural treatment at first, and his developmental retardation became increasingly accentuated in his first year of life. He could not turn over and he uttered only a few lallings. He showed abnormal posturing with arched his back induced by emotional changes or subtle stimulation. Severe foot clonus was also evoked easily by only touching his lower extremities. In addition, the spasticity and muscle weakness of the lower extremities progressed. The patient needed tube feeding owing to dysphagia, and he experienced severe bronchitis 5 times and a generalised convulsive seizure. At 12 months of age, CT revealed a new lesion in an ischial bone in addition to the lesions in the liver, kidney and lungs. The lesions in the right lung became enlarged. MRI revealed that the CNS lesions had also become progressed (Fig.1 E, F). The NGS-based CGP test, FoundationOne$^{?}$ CDx was peformed on the specimens obtained from the cutaneous lesion. KIF5B-ALK fusion was identified as an activating mutation. Administration of an ALK-inhibitor for the patient was discussed in the molecular tumour board called 'expert panel', and approved by the institutional clinical review board for off-label use. After obtaining informed consent from parents, the patient was given alectinib at 16 months of age. Two months after the initiation of alectinib administration, the subcutaneous lesions decreased in size. MRI revealed that the lesions of the medulla and cerebellum achieved complete regression (Fig. 1G). The lesion in the cervico-thoracic spinal cord also regressed (Fig. 1 H). The patient's condition improved, and he started ingestion of food orally and could say a few sentences. The spasticity and clonus of the extremities were relieved. For the 3 months treatment periods, adverse events were only observed the localized eczema and fever evaluated as grade 1 according to the Common Terminology Criteria for Adverse Events version 5.0.

Discussion

ALK is a tyrosine kinase gene located on chromosome 2p23, and its rearrangement is identified for the first time in non-Hodgkin's lymphoma in 1994 by Morris et al. [5] In non-small cell lung cancer (NSCLC), EML4-ALK fusion was detected in 2007[6]and has been considered as a target of tyrosine kinase inhibitors. In addition, KIF5B-ALK fusion is also identified in NSCLC in 2009.[7] Recently, some cases of KIF5B-ALK fusion have been reported in histiocytosis, including JXG.[8-12]Several teenage patients and adults with KIF5B-ALK fusion were treated with ALK inhibitor.[10-12] Chang et al[11] presented the case of a 15-year-old male patient with histiocytosis affected cavernous sinus. He received crizotinib therapy, and the lesion resolved 3 months later. However, no case has been reported in infants with histiocytic neoplasm treated with ALK inhibitors.

Several ALK inhibitors, including crizotinib, alectinib, and ceritinib, have been approved mainly for NSCLC in Japan. Crizotinib has been administered for paediatric patients with anaplastic large cell lymphoma (ALCL) and solid tumours, including neuroblastoma, and its tolerability and safety have been established.[13,14] Alectinib was indicated to show a favourable clinical activity and was well tolerated by paediatric patients with ALK-positive ALCL that progressed under conventional chemotherapy.[15,16] In addition, alectinib had superior CNS activity and significantly delayed the progression of CNS metastases as compared with crizotinib in patients with advanced ALK-positive NSCLC.[17]Among these ALK inhibitors, we selected alectinib for the present case because the CNS lesions were most critical lesions in this patient.

Actionable targets, including ALK fusion, are screened on the NGS-based CGP tests covered by the national health insurance system for refractory and recurrent solid tumours in Japan. Actionable targets have also been revealed in paediatric patients. Although most of the drugs corresponding to the target genes are off-labelled in paediatric patients, it is estimated that the effect of the molecular target agents is superior, and adverse events and late complications are not more severe than those in patients treated with conventional anticancer drugs.[18,19] Since the comprehensive genomic analysis by whole-exome and transcriptome haematological malignancies, actionable targets could also be identified in histiocytic neoplasms,[3,4] including

JXG and LCH which tend to arise in neonates.[1,2,20] The administration of these molecular target agents may be preferable for those patients with actionable targets to conventional chemotherapy. It is possible that histiocytosis will be classified according to its activating mutations in the near future, which directly link to targeted therapy.

The present patient with systemic JXG who had KIF5B-ALK fusion achieved clinical improvement with alectinib therapy. A high index of cognition should be appreciated for such an actionable target in histiocytic neoplasms.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Legends

Figure 1. (A) A retroauricular subcutaneous nodule. (B) Enhanced computed tomograohy image showing peri-pleural nodular shadows mainly in the right lung field. (C) Multiple low-density areas in the liver. (D) Multiple low-density areas of approximately 1.0 cm in diameter in the right kidney. (E) Enhanced magnetic resonance images of the lesions of the medulla and cerebellar hemisphere and (F) the massive tumour in the spinal cord from the level of the atlas to the upper thoracic spine before the initiation of alectinib therapy. (G) Complete regression of the lesions of the medulla and cerebellum 2 months after the initiation of alectinib therapy. (H) The lesions of the spinal cord also regressed.

Figure 2. (A) Histological examination (HE; haematoxylin-eosin) result of the biopsy specimen from the cutaneous lesion. (B) The spindle cells with circular unequal nucleus and light cytoplasm. (C) Increased tumor cells between the dermal collagen fibres. (D) The spindle cells showing positivity for ALK1 antibody and (E, F) positivity for ALK D5F3 by immunohistological tests.