EDITORIAL

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Frequent detection of genetic aberrations reveals novel pathogenesis and treatment modalities in systemic juvenile xanthogranuloma

Juvenile xanthogranuloma (JXG), the most common form of non-Langerhans cell histiocytosis (non-LCH), is generally confined to the skin during infancy and early childhood.[1] JXG rarely involves extracutaneous tissues or systemic organs, resulting in high morbidity and mortality rates. Clonality in JXG has been verified by histopathological and genetic analyses, which have shown it to be tumorous rather than a reactive disorder of JXG.[2] However, the exact etiopathogenesis of JXG remains unclear.

Diverse organs and systems can be involved in systemic JXG (SJXG). The most common extracutaneous sites include the eyes, central nervous system (CNS), liver, and lungs. Compared with cutaneous JXG, SJXG usually requires more aggressive treatment. Conventionally, the first-line treatment for SJXG is based on chemotherapy used in Langerhans cell histiocytosis (LCH), such as corticosteroids and vinblastine, with various responses.[3] Alternative regimens include methotrexate, cladribine, and cytarabine when initial chemotherapy fails.

In the past decade, genomic studies have been conducted on histiocytosis, including JXG, and distinctive genetic abnormalities have been discovered (e.g., *BRAFV600E* mutations and *ALK* translocations).[4,5] These novel genetic discoveries further confirmed the tumorigenesis of JXG and highlighted the possibility of therapeutic targets in refractory or severe cases.

GENETIC ABERRATIONS IN THE PATHOGENESIS OF SJXG

JXG is involved in the clonal proliferation of histiocytes by human androgen receptor assay (HUMARA).[2] However, the drivers of cell proliferation in JXG remain to be elucidated. Several cases of JXG have been reported in children with germline mutations in *NF1* or *NF2*, as well as with coincident juvenile myelomonocytic leukemia, showing its association with the myeloid lineage and gene mutations.[6] Some studies reported concomitant JXG and LCH, suggesting the presence of a common progenitor.[7] Genetic evaluation of JXG showed more complexity in advanced JXG than in cutaneous JXG, indicating a different pathogenesis between them.[8]

In 2010, Badalian-Very et al.[9] first reported that patients with LCH harbored the *BRAFV600E* mutation, creating a new path for molecular research on histiocytosis. A high frequency of *BRAFV600E* mutation was found in more than 50% of LCH and Erdheim-Chester disease (ECD) cases. Other abnormalities in *MAP2K1* and *MET* genes, which are all related to mitogen-activated protein kinase (MAPK) pathway activation, were also detected.

Genomic studies are increasingly involving JXG, although they are limited by its rarity. Interestingly, *BRAFV600E* mutations were also detected in JXG, but mainly in JXG lesions concurrent with LCH or in SJXG with CNS or ocular involvement.[7,10,11] Cutaneous and oral JXG cases seldom harbor the *BRAFV600E* mutation.[12,13] Other mutations of *KRAS* and *MAP2K1* have also been identified in SJXG with voluminous neck tumors and hematologic involvement, respectively.[5] Similar to LCH and ECD, the abovementioned genetic abnormalities are mainly involved in the MAPK signaling pathway, showing its association with the pathogenesis of SJXG.

Recurrent mutations in *PIK3CA* have been described in ECD and occasionally in LCH, which activate the PI3K pathway. Instead, *PI3KCD* mutations have been detected in several cases of JXG, indicating that this signaling pathway is also involved in the pathogenesis of JXG.[14] Durham

DOI: 10.1002/ped4.12398

et al.[15] have reported activating mutations in *CSF1R* in patients with aggressive JXG. Moreover, *CSF1R* mutations observed in two monozygotic twins, which were wild-type in their blood and fingernails, suggested that histiocytosis may arise from mutations of extraembryonic macrophage progenitors.

Besides gene mutations, gene translocations have been found in systemic histiocytosis. Wolter et al.[16] reported a case of JXG with subglottic involvement harboring an anaplastic lymphoma kinase (*ALK*) gene translocation. Chang et al.[17] reported ALK expression in a rare subtype of histiocytic neoplasm in three infants with involvement of the liver and hematopoietic system. Subsequently, more cases of histiocytosis, especially those with CNS involvement, were reported with *ALK* translocation and ALK immunostaining.[18] These findings reveal that ALK is an important driver in the pathogenesis of histiocytosis, including that of SJXG. ALK was first described in anaplastic large-cell lymphoma and was later found in a set of tumors, and it is a proto-oncogene activated during tumorigenesis. Interestingly, upregulation of ALK phosphorylation promoted the phosphorylation of PI3K/AKT, STAT3, and MEK/ERK, indicating that ALK induces cellular hyperplasia through various signaling pathways.[5] Additional studies have identified *MRC1-PDGFRB, RNF11-BRAF*, and *MYH9-FLT3* fusion proteins in SJXG.[5,19]

As recurrent *BRAFV600E* mutations and *ALK* translocations have been detected in histiocytosis, we collected 23 cases of SJXG to screen for two common types of genetic abnormalities in a recent study, and the results showed that 34.7% (8/23) of these cases harbored *ALK* translocations and 17.4% (4/23) carried *BRAFV600E* mutants.[12] Our study indicates that *ALK* translocations play an important role in the pathogenesis of SJXG, which is different from *BRAFV600E* mutations in LCH and ECD. However, gene alterations were unknown in up to 50% of the SJXG cases in our study, and further studies using broad molecular assays are needed.

THE TREATMENT MODALITIES IN SJXG

Although few cases of SJXG appear to resolve spontaneously, multisystem JXG treatment has been suggested. SJXG with ocular involvement is associated with a high incidence of glaucoma and usually requires early intervention. The prognosis of patients with SJXG with liver, CNS, and hematological involvement is poor and requires prompt management.

Currently, no guidelines exist for the management of SJXG. Traditionally, the first-line treatment of choice has been LCH-based chemotherapy (vinblastine, prednisone, and mercaptopurine) for SJXG. There have also been reports on the successful use of cladribine and cytarabine for treating SJXG with CNS involvement.[20] Other management options include surgery, radiotherapy, and high doses of corticosteroids, cyclosporin A, methotrexate, and etoposide, all of which require greater awareness of their side effects when selected, especially in infancy and early childhood.

The discovery of recurrent activating mutations and translocations highlights the potential for targeted inhibition in subsets of patients with JXG bearing these alterations, especially in refractory diseases.[21] Zhang et al.[11] reported a patient with SJXG who received a trial of anti-BRAF targeted therapy (dabrafenib) and showed significant regression of both ocular and systemic lesions. Another child with an aggressive and refractory BRAFV600E-positive multifocal CNS-JXG responded dramatically to dabrafenib.[10] Our previous study showed a good response to the BRAFV600E inhibitor (vemurofenib) in CNS-SJXG cases that failed initial chemotherapy. Other MEK inhibitors specific for *MAP2K1* mutations have successfully treated severe SJXG.[5]

Most cases of ALK-positive histiocytosis have been treated with oral ALK inhibitors such as crizotinib and alectinib, achieving promising effects. Alectinib has been reported to show favorable clinical activity and is well-tolerated by pediatric patients with ALK-positive anaplastic large-cell lymphoma who progressed under conventional chemotherapy. A notable therapeutic response to alectinib was also noted in a patient with SJXG with *ALK* translocation.[22] In one case report, two months after initiating alectinib administration, the subcutaneous lesions decreased in size.[23] In addition, alectinib can pass through the brain-blood barrier and is more effective than crizotinib against CNS lesions in JXG. The only side effects observed were mild eczema and transient fever.[24] Hematopoietic stem cell transplantation may be another treatment option for refractory SJXG, in which the reconstruction of hematopoietic stem cells helps normalize histiocyte differentiation.[25] Ito et al.[26] reported a case of SJXG with bone involvement and multiple pathological fractures refractory to chemotherapy and ultimately treated with haploidentical hematopoietic stem cell transplantation. Another report showed a rapid clinical response to dasatinib in a child with SJXG with *MRC1-PDGFRB* translocation.[27] Topical rapamycin, which targets the PI3K/mTOR pathway, was successfully administered to the JXG lesions.[28]

Our commentary highlights the importance of complete genomic profiling, including mutant signal pathways and translocations involved in cell proliferation. This reveals the novel pathogenesis of SJXG and guides the use of targeted agents, particularly for patients who fail to respond to conventional therapies. Due to the rarity of SJXG, genomic

studies should be conducted worldwide to identify its exact targets with minimal side effects.

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CONFLICT OF INTEREST

None.

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How to cite this article: Xu J, Ma H, Yao X, Han X, Wen Y, Wang S, et al. Frequent detection of genetic aberrations reveals novel pathogenesis and treatment modalities in systemic juvenile xanthogranuloma. *Pediatr Investig*. 2023;7:212–215. https://doi.org/10.1002/ped4.12398