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Successful treatment of systemic juvenile xanthogranuloma with an *ABL2::GAB2* fusion using dasatinib after failure of conventional chemotherapy and MEK inhibition

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Juvenile xanthogranuloma (JXG) is a non-Langerhans cell histiocytosis with a broad clinical spectrum, ranging from self-limited skin lesions to life-threatening systemic involvement. Recurrent kinase-activating fusions, including *NTRK1*[1], *CLTC::SYK*[2], *MRC1::PDGFRB*[3] and *GAB2::BRAF*[4], have been identified in JXG, providing a rationale for targeted therapy. However, optimal management for patients without these common fusions remains challenging. Here we report a case of systemic JXG harboring a novel *ABL2::GAB2* fusion that was refractory to conventional chemotherapy and MEK inhibition but responded dramatically to dasatinib, an ABL inhibitor.

A 13-month-old girl presented with skin rash and recurrent fever since 2 months of age. The cutaneous lesions were red-to-brownish papules, progressively increasing in number and size (up to 1 cm). Systemic involvement developed rapidly, including hepatosplenomegaly, liver dysfunction, ascites, multiple osteolytic lesions (skull) (Figure 1A), pulmonary interstitial disease with pleural effusion, and bile duct involvement. Skin biopsy showed diffuse dermal infiltration of foamy histiocytes with CD68 positivity and negativity for CD1a, Langerin, S-100, and ALK, consistent with JXG. No Touton giant cells were seen. Bronchoscopy revealed yellowish granulomatous lesions in multiple bronchial segments of both lungs (Figure 1B), and biopsy of the bronchial wall showed chronic inflammation with scattered chronic inflammatory cells and alveolar macrophages, further supporting the diagnosis of pulmonary involvement.

The patient was initially treated with an LCH-III regimen (vinblastine/prednisone) without response. Subsequently, trametinib (a MEK inhibitor, 0.025 mg/kg/day) was added for 10 days, which only transiently reduced liver/spleen size without improving thrombocytopenia or ascites. Chemotherapy was resumed and later combined again with trametinib, but the disease continued to progress. Sirolimus (trough level >7 ng/ml) for over one month had been attempted at the outside hospital but also failed, and was not resumed after the patient was transferred to our center. Extensive work-up including whole-genome sequencing (blood) and targeted gene panel (lesional tissue) revealed no known LCH-associated mutations. However, transcriptome sequencing of skin biopsy tissue identified an in-frame *ABL2::GAB2* fusion (Figure 1C). Total RNA was extracted from fresh skin biopsy tissue using the RNApure Blood Kit (CWBIO, Jiangsu, China). Stranded mRNA sequencing libraries were constructed using the VAHTS Stranded mRNA-seq Library Prep Kit for Illumina (Vazyme, Nanjing, China), and sequencing was performed on an Illumina NovaSeq X platform with paired-end 150-bp reads. After quality control and trimming using fastp[5], the clean reads were aligned to the hg19 human reference genome using STAR. Fusion calling was performed using Arriba[6], and candidate fusions were manually reviewed using Integrative Genomics Viewer (IGV)[7] and confirmed by Sanger sequencing. The fusion was absent in bone marrow and peripheral blood by RT-qPCR, indicating a somatic lesion-restricted event. This fusion has never been reported in JXG; only a single case in another tumor type has been described, with no treatment information.

Given the refractoriness to conventional therapy and the presence of the *ABL2::GAB2* fusion—which involves the ABL2 kinase domain—we initiated dasatinib (an ABL inhibitor) at 20 mg/day, later reduced to 10 mg/day due to microscopic hematuria and high drug levels. Remarkably, within weeks, the patient's skin lesions, pulmonary infiltrates and pleural effusion,

and hepatosplenomegaly showed progressive improvement (Figure 2). Liver enzymes and bilirubin normalized, and she remained afebrile thereafter. Serial assessments demonstrated complete disappearance of renal lesions by 1.5 months after treatment initiation. At the last follow-up (8 months after dasatinib initiation), the child remained clinically well with sustained radiological response. This study was approved by the Ethics Committee of Capital Institute of Pediatrics (approval number: SHERLL2025132). All procedures followed the principles of the Declaration of Helsinki. The patient's parents provided written informed consent in Chinese for publication of this case report and any accompanying images.

Our case expands the genetic landscape of JXG by identifying *ABL2::GAB2* as a novel fusion. While *GAB2::BRAF* was recently reported in disseminated JXG responsive to trametinib[4], our fusion partners are distinct: ABL2 (a non-receptor tyrosine kinase) fused to GAB2 (an adaptor protein). The transforming potential of *ABL2::GAB2* is supported by its absence in normal tissues and the dramatic response to dasatinib, an ABL inhibitor. Since the fusion involves the ABL2 kinase domain, dasatinib was selected over imatinib based on both structural and pharmacological evidence. The co-crystal structure of ABL2 with dasatinib confirms that dasatinib directly binds and inhibits ABL2 kinase activity[8]. Furthermore, studies on ABL-class leukemias have demonstrated that the specific kinase type determines TKI sensitivity, with ABL2 fusions showing potent responses to second-generation TKIs such as dasatinib[9]. Recent studies have further expanded the therapeutic options for JXG: Wang et al. reported successful use of dabrafenib in a chemotherapy-refractory pediatric JXG harboring a BRAF mutation[10], and Geerlinks et al. systematically reviewed the role of MAPK pathway inhibitors in histiocytic disorders[11]. Additionally, Diamond et al. demonstrated the efficacy of MEK inhibition across a spectrum of histiocytic neoplasms, establishing MAPK blockade as a cornerstone of targeted therapy[12]. However, our case demonstrates that not all JXG fusions are MEK-dependent; our patient failed trametinib but responded to dasatinib, highlighting the importance of precise molecular diagnosis. Notably, a recent report of a *GAB1-ABL2* fusion in an infant-type glioma also showed response to dasatinib[13], further supporting that *ABL2* fusions are actionable drivers across tumor types. Moreover, Fragneau et al. comprehensively characterized *NTRK1*-rearranged histiocytosis, demonstrating a diverse clinicopathological spectrum and potential responsiveness to TRK inhibition[14], underscoring the growing recognition that diverse kinase fusions drive these diseases and may be amenable to specific targeted inhibitors[15]. To our knowledge, this is the first successful use of dasatinib in JXG, providing a new therapeutic option for ABL-pathway driven disease. In the broader context of histiocytic neoplasms, MAPK pathway inhibitors have become a cornerstone of targeted therapy[11,12], but our case emphasizes that comprehensive genomic profiling is essential to identify non-MAPK drivers that may respond to alternative targeted agents.

In conclusion, we report the first case of systemic JXG harboring an *ABL2::GAB2* fusion, which was resistant to chemotherapy, trametinib and sirolimus, but achieved reversal with dasatinib. Our findings highlight the critical role of genomic profiling in guiding precision therapy for refractory histiocytosis.

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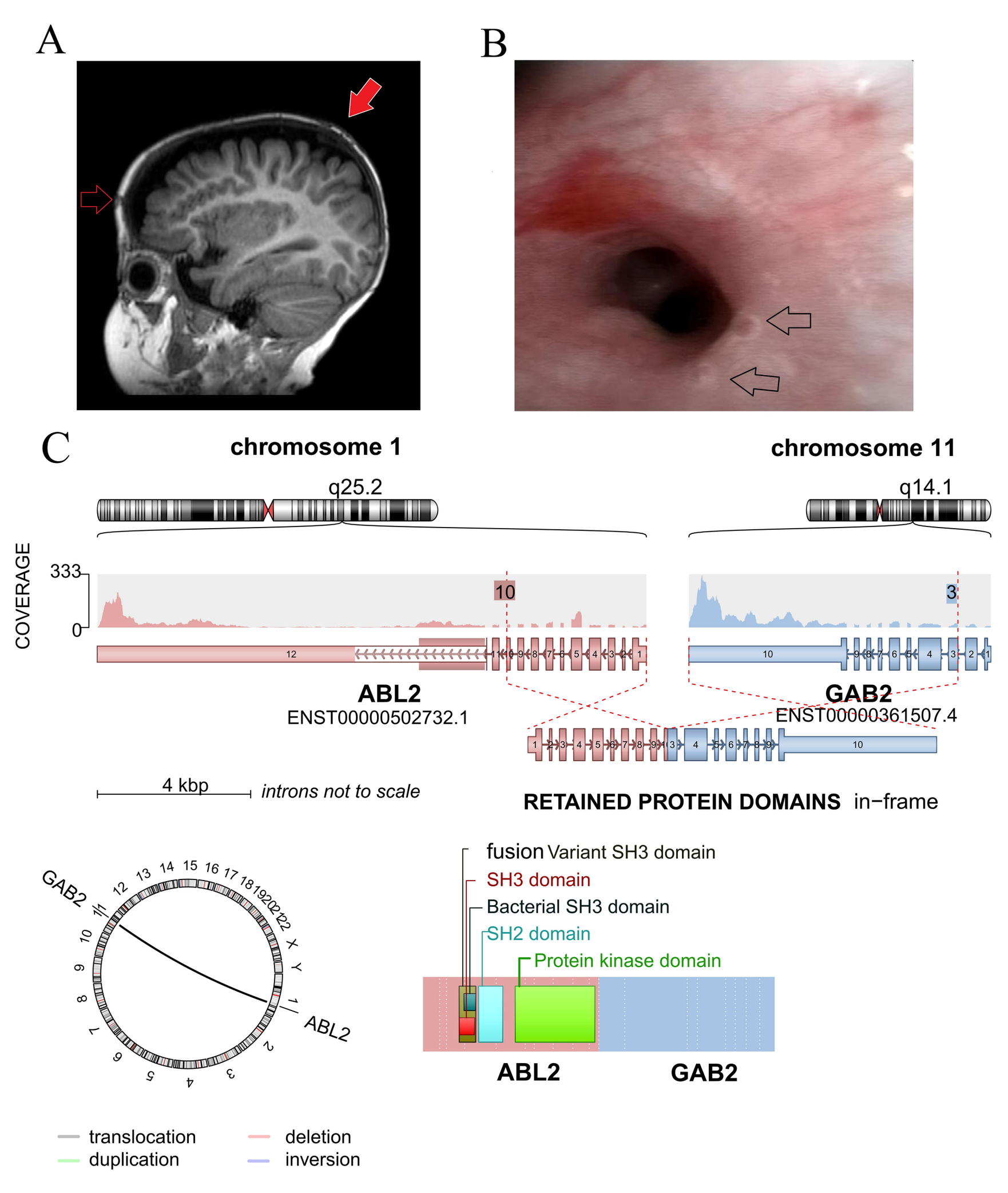
Figure legend

Figure 1 Diagnostic imaging and molecular identification of systemic JXG. (A) Cranial MRI (sagittal T1-weighted image) showing osteolytic lesions of the skull (red arrow). (B) Bronchoscopic view of the left bronchial lingular segment mucosal lesion (black arrow). (C) Identification of the *ABL2::GAB2* fusion by transcriptome sequencing of the skin biopsy tissue. Total RNA was extracted and subjected to stranded mRNA library preparation and paired-end 150-bp sequencing on the Illumina NovaSeq X platform. Fusion calling was performed using Arriba and STAR-Fusion, and the candidate fusion was manually verified with Integrative Genomics Viewer and confirmed by Sanger sequencing.

Figure 2 Clinical and radiological response to dasatinib treatment. Panels A–D show baseline findings: (A) abdominal skin lesions; (B) left axillary skin lesions; (C) pulmonary infiltrates and pleural effusion on chest CT; (D) renal lesions on MRI. Panels E–H and I–L show the corresponding improvement at 1.5 months and 8 months after treatment initiation, respectively, with complete disappearance of renal lesions by 1.5 months and sustained improvement at 8 months.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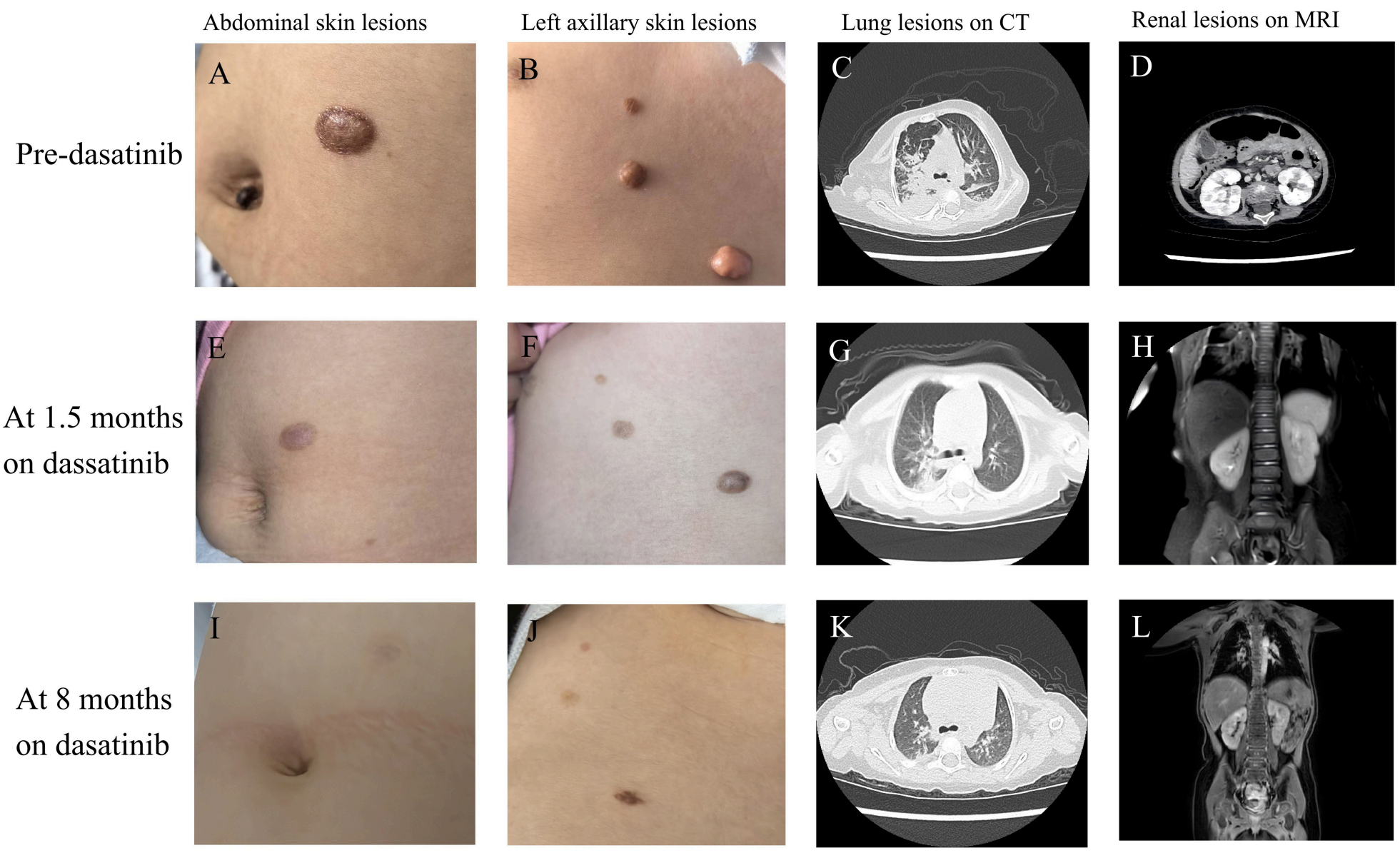
Abdominal skin lesions
Left axillary skin lesions
Lung lesions on CT
Renal lesions on MRI
Pre-dasatinib
At 1.5 months on dassatinib
At 8 months on dasatinib
A
B
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