Multiple cutaneous nodules in a 7-month-old boy

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Research

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Abstract

Objective Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disease and has many manifestations involves virtually any organ. In this study, we report a TSC patient with new type skin lesions.

Methods The 7-month-old patient had cardiac rhabdomyoma, subependymal giant cell astrocytoma (SEGA) and hypomelanotic macules. He presented with a 2-month history of gradual growth multiple cutaneous nodules. We performed biopsy of cutaneous nodules and whole-exome sequencing in both paraffin block tissue and blood samples.

Results The pathological finding of cutaneous nodules was consistent with juvenile xanthogranuloma (JXG). The whole-exome sequencing identified TSC1 (c.2356C>T, p.R786*) mutation in both paraffin block tissue and blood samples. Based on both clinical signs and genetic testing, our patient was definitely diagnosed with TSC and JXG was a new type of skin lesions in TSC. The symptoms improved significantly especially the JXG skin lesions after the treatment of sirolimus.

Conclusion This is the first report of JXG skin lesions in TSC patient. Genetic testing is necessary in JXG. These findings expand the phenotype of skin in TSC and pave the way toward an understanding of the pathogenesis and treatment of JXG.

Background

TSC is a rare autosomal dominant genetic disease with an incidence rate of approximately 1/6000[(1)]. TSC has many manifestations involves virtually any organ in the body, and the most common findings are benign tumors of the skin, brain, heart, kidneys and lung. Skin lesions include hypomelanotic macules (90% of patients), facial angiofibromas (75% of patients), fibrous cephalic plaques (25% of patients) and shagreen patches (> 50% of patients)(1). Study has reported that the use of sirolimus on specific TSC manifestations(2–4).

JXG is a common form of non-Langerhans cell histiocytosis in infants and children, characterized by spontaneous formation of cutaneous nodules on the scalp, face trunk, and extremities. Approximately 71% of JXG cases occur in the first year of life (5). The pathogenesis of JXG is unknown.

Here we report a 7-month-old TSC boy presented with a 2-month history of gradual growth multiple cutaneous nodules, which through biopsy and whole-exome sequencing finally identified JXG as a new type of skin lesions in TSC.

Method

Clinical course and diagnosis

A 7-month-old boy was referred to our hospital for multiple cutaneous nodules. At the fifth month, cutaneous nodules first appeared behind the right ear without evident cause or tenderness and gradually growth multiple nodules. During consultation in our department, physical examination showed multiple nodules on the scalp, eyelids, trunk, and limbs of the patient which are papules or yellow and erythematous nodules without inflammation or ulceration (Figs. 1A-B). He had one hypomelanotic macule on the abdomen (Fig. 1B). One week before birth, examination revealed a strong echo mass in the heart of the fetus (patient), indicating cardiac rhabdomyoma. A regular follow-up to observe changes of cardiac rhabdomyoma was recommended.

Brain computed tomography (CT) showed multiple punctate, flaky, and round-like high-density holes in the bilateral lateral ventricles and bilateral subependymal. A large lesion (51 mm × 46 mm) located in the posterior corner of the left lateral ventricle was diagnosed as SEGA (Fig. 2A). Head magnetic resonance imaging (MRI) showed nodules in the posterior corners of bilateral ventricles on T1- and T2-weighted images (Figs. 2B–C). Chest CT showed pulmonary subpleural nodule in the lower left lobe (Fig. 2D). Cardiac ultrasound showed cardiac rhabdomyoma in the left ventricular cavity which was approximately 15 mm × 12 mm. Abdominal ultrasonography was normal. Ophthalmologic evaluation was not performed because the patient was too young to cooperatate. On laboratory blood tests the patient had normal lipid. He had no facial angiofibromas, shagreen patches or seizures and the development was normal.

The patient’s mother had seizures since four years old. During pregnancy, she took lamotrigine and valpromide tablets but still had seizures every month. She had multiple skin lesions, including hypomelanotic macules, shagreen patches, and facial angiofibromas. The patient’s uncle had seizures and died of “brain tumor” at the age of 25 years. The patient’s grandfather had hypomelanotic macules, shagreen patches and facial angiofibromas.

We performed biopsy of cutaneous nodules. Paraffin block tissue and whole blood samples were collected from existing family members to obtain genomic DNA for whole-exome sequencing.

The diagnosis was made by at least two experienced specialists based on the 2012 TSC Consensus Conference updated diagnostic criteria(6). We obtained written consent from parents. This study was approved by the Ethics Committee of Chinese PLA General Hospital (Beijing, China).

Results

Histopathological examination showed typical histiocytosis in the dermis, with the presence of many multinucleated giant cells and inflammatory cells (Figs. 3A–B). Cluster differentiation 68 (CD68) and CD163 were positive (Figs. 3C–D) and S100, CD1a, langerin, human melanoma black 45 (HMB-45) and Melan-A were negative in immunohistochemical stainings (Figs. 3E, 3F, 3G, and 3I). The Ki-67 (Fig. 3H) proliferation index was 15%. The pathological finding of cutaneous nodules is consistent with JXG.

We further performed whole-exome sequencing and identified TSC1 mutation (c.2356C > T, p.R786*) in both paraffin block tissue and blood samples (Fig. 1E). This mutation was also found in blood of his mother and grandfather (Fig. 1E). The nonsense mutation has been reported in study(7). No other disease-causing mutations were found. Based on both clinical signs and genetic testing, our patient is definitely diagnosed with TSC. Here, we consider JXG to be a new skin lesion of TSC.

We gave the patient sirolimos orally at the age of eight months. The initial dose of sirolimus was 1 mg/(m^2·day) and adjusted according to the blood concentration to maintain the blood concentration at 5–10 μg/L. He has oral sirolimus regularly for 1 year. Sirolimus was well tolerated without evident adverse reactions. After three months of sirolimus, the multiple nodules disappeared and hypomelanotic macule in the abdomen was no change (Figs. 1C-D). After one year of sirolimus, cardiac ultrasound showed reduction of cardiac rhabdomyoma in the left ventricular cavity (2 mm × 4 mm). Blood routine, liver functions, kidney functions and serum electrolytes were normal. The patient continued oral sirolimus and followed up regularly every six months.

Discussion

Regarding to cutaneous nodules, a broad spectrum of differential diagnosis should be taken into account by immunohistochemical staining. S100, CD1a, Langerin are negative, which is distinguished from Langerhans cell histiocytosis. S-100, HMB-45 and Melan-A are negative, which is distinguished from malignant melanoma. The pathological finding is consistent with JXG.

Through whole-exome sequencing in paraffin block tissue, we overturned the original pathological diagnosis and finally identified JXG as a new type of skin lesions in TSC. The pathogenesis of JXG is unknown. Previously reported patients with JXG have not performed whole-exome gene sequencing, thus, no TSC1 or TSC2 mutations have been reported in JXG patients. Through this case, we recommend that JXG patients should perform histopathological examination as well as genetic testing.

The etiology of TSC involves the mutation in TSC1 (9q34, encoding hamartin) or TSC2 (16p13.3, encoding tuberin). Hamartin and tuberin form a functional unit that is involved in inhibiting the mammalian target of rapamycin (mTOR) pathway(8). Sirolimus selectively inhibits mTOR signaling. Clinical trials and scientific evidence support the use of sirolimus in TSC patients with specific manifestations, including SEGA and skin lesions(2–4). Darcy AK et al. conducted a multicenter clinical investigation on the safety of mTOR inhibitors in TSC patients before the age of two years(9). Sirolimus has been reported to treat fetus with TSC presenting cardiac rhabdomyoma(10). Our patient started sirolimus treatment at the age of eight months and the symptoms improved significantly, especially the JXG skin lesions.

The patient had pulmonary isolated subpleural nodule in the left lower lobe via chest CT. The round mass in pulmonary nodules could be a sign of lung tumors or lesions. The lesion was not confirmed because the patient's parents refused the lung biopsy. Annual CT test was recommended to the patient.

Conclusion

To the best of our knowledge, this is the first report of JXG skin lesions in TSC patient. Genetic testing is necessary in JXG. These findings expand the phenotype of skin in TSC and pave the way toward an understanding of the pathogenesis and treatment of JXG.

Abbreviations

JXG: juvenile xanthogranuloma; TSC: tuberous sclerosis complex; SEGA: sub-ependymal giant cell astrocytoma; CT: computed tomography; MRI: magnetic resonance imaging; CD68: cluster differentiation 68; HMB45: Langerin, human melanoma black 45; mTOR: mammalian target of rapamycin.

Declarations

Ethics approval and consent to participate

This study is performed according the international rules of acceptable clinical trials, and informed consent is obtained from the parents of the patient.

Consent for publication

The parents of the patient have signed consent for publication.

Availability of data and materials

All the data in this study were included in the published article.

Competing interests

The authors report no disclosures relevant to the manuscript.

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Authors' contributions

QL and LPZ participated in the study design, clinical evaluation of patients, data analysis, and manuscript drafting. XYS contributed in the data analysis and manuscript drafting. YYW, MNZ, WZW, JW, QHW and HMC conducted data collection. All authors read and approved the final manuscript.

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Figures

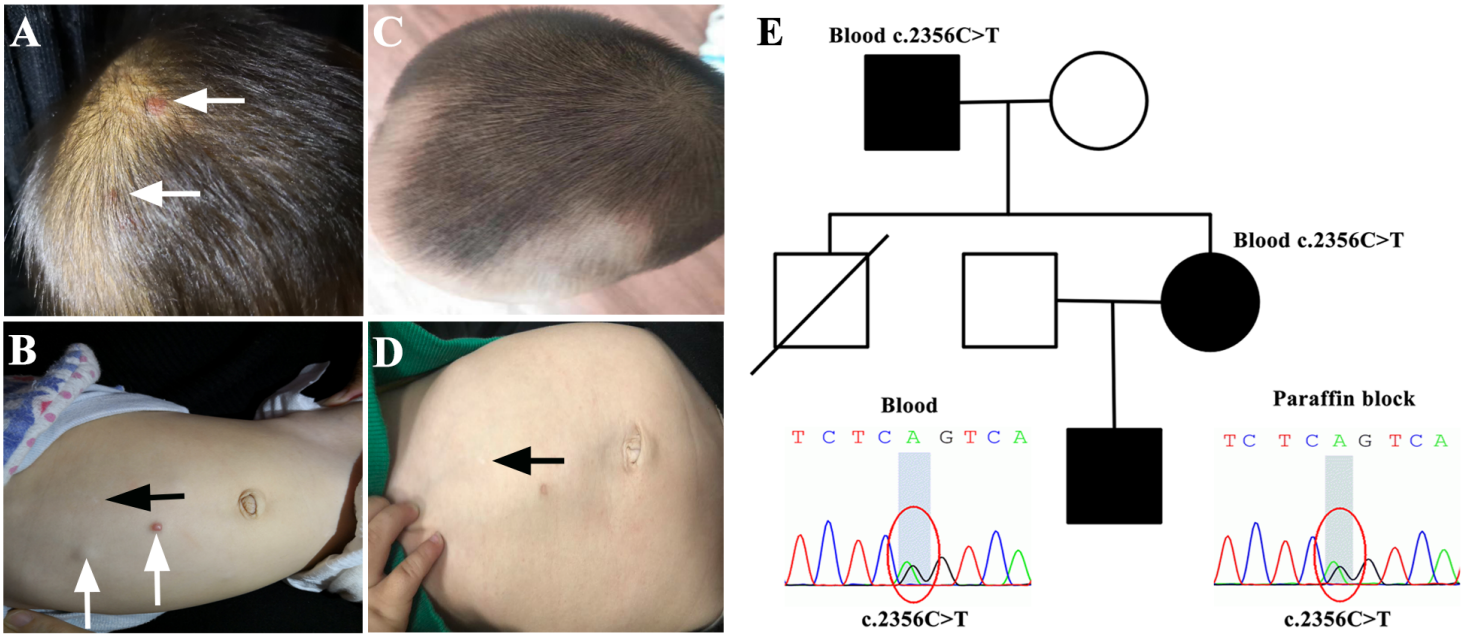

Figure 1

A-B) Nodules on the scalp and abdomen (white arrow) and hypomelanotic macule on the abdomen(black arrow) before treatment. C-D) The multiple nodules disappeared and hypomelanotic macule in the abdomen was no change (black arrow) after three months of sirolimus. E) Family pedigree. The black square indicates TSC patient. The square with slash indicates the person is died. Sequence chromatograms show TSC1 mutation (c.2356C>T, p.R786*) in both paraffin block tissue and blood samples. The mutation is also found in blood of his mother and grandfather.

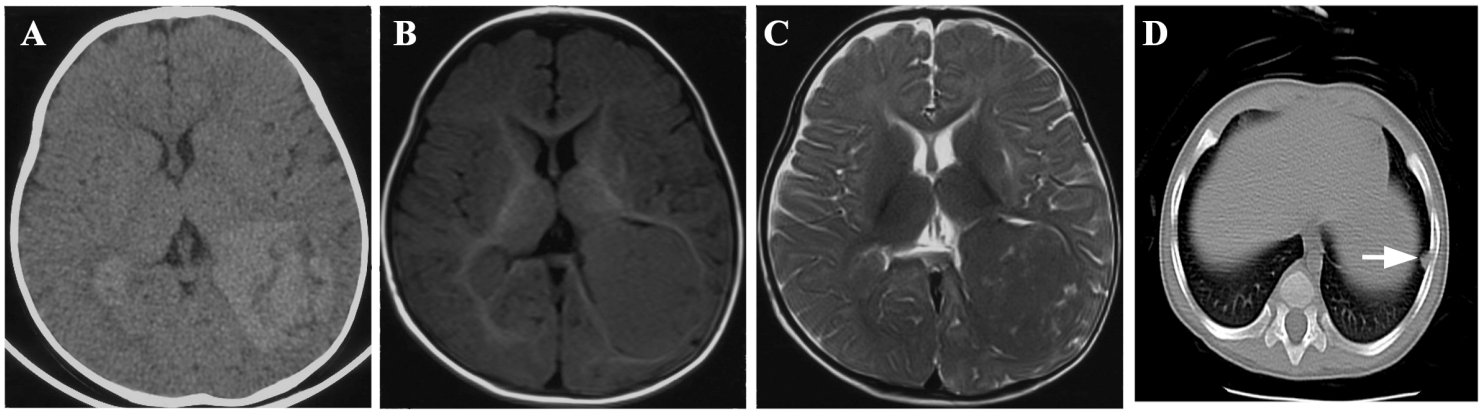

Figure 2

A) Brain CT shows multiple punctate, flaky, and round-like high-density holes in the bilateral lateral ventricles and bilateral subependymal. A large lesion located in the posterior corner of the left lateral ventricle was diagnosed as SEGA. B-C) Head MRI shows nodules in the posterior corners of bilateral ventricles on T1- and T2-weighted images. D) Chest CT showed pulmonary subpleural nodule (white arrow).

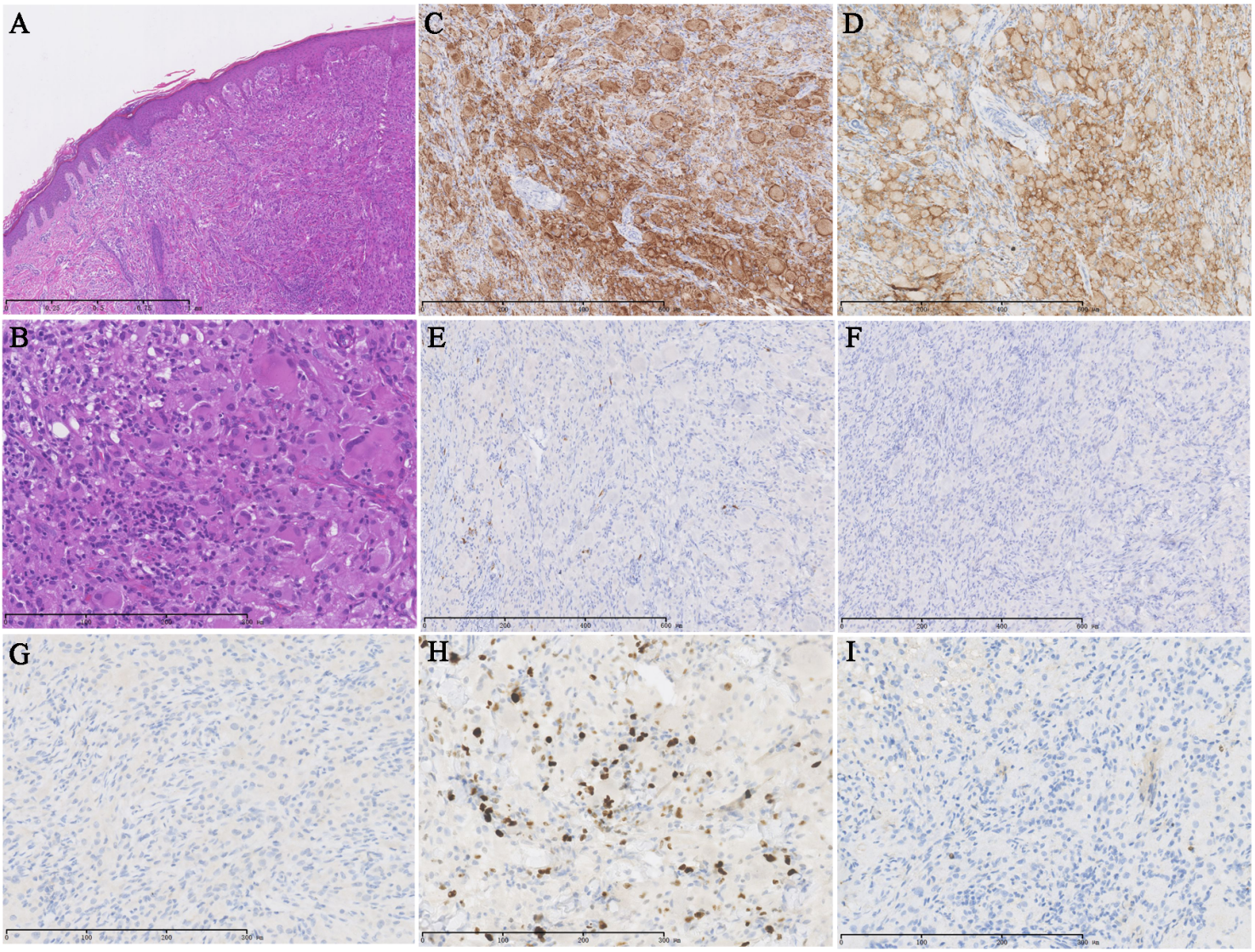

Figure 3

Histomorphologic examination. A-B) show typical histiocytosis findings in the dermis, with the presence of many multinucleated giant cells and inflammatory cells. C-I) show immunostainings results that are positive for CD68 (C) and CD168 (D). S-100 (E), CD1a (F), Lagerin (G) and Melan-A (I) are negative. The Ki-67 proliferation index is 15% (H).