Rare Association of Tuberous sclerosis with Acute Lymphoblastic Leukemia: Case Report with Review of Literature

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Abstract

Acute lymphoblastic leukemia (ALL) is the most common leukemia in children in which 85% of all cases are of B-cell ALL and approximately 15% cases are of T-cell ALL (T-ALL). Recent revolution in next-generation sequencing has uncovered many novel somatic mutations and rearrangements in ALL cells, which have prognostic and therapeutic implications, and it has also led to recognition of germline variants in the same genes with somatic mutations commonly associated with ALL. Apart from increasing the risk of developing ALL, germline variants may influence diagnostic testing, genetic counseling, and response to antileukemic treatment. This emphasizes importance of identification of new germline variants, or association of inherited syndromes with ALL or other malignancies. Down’s syndrome, Shwachman’s syndrome, Fanconi anemia, Bloom’s syndrome, neurofibromatosis, and ataxia telangiectasia are well-recognized conditions associated with ALL. In this communication, we report a rare association of T-ALL with tuberous sclerosis (TS). This is the first reported case, showing association of T cell leukemia and TS with confirmatory genetic work-up.

Keywords

► acute lymphoblastic leukemia
► neurocutaneous syndromes
► tuberous sclerosis

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy with peak incidence in children between 2 and 9 years of age.1 Recent revolution in next-generation sequencing has uncovered many novel somatic mutations and rearrangements in ALL cells, which have prognostic and therapeutic implications.2,3 Similarly, it has led to recognition of germline variants in the same genes (e.g., PAX5, ETV6, and IKZF1) with somatic mutations commonly associated with ALL (►Table 1).4,5 Apart from increasing the risk of developing ALL, germline variants may influence diagnostic testing, genetic counseling, and response to antileukemic treatment. This emphasizes importance of identification of new germline variants, or association of inherited syndromes with ALL or other malignancies. Down’s syndrome, Shwachman’s syndrome, Fanconi anemia, Bloom’s syndrome, neurofibromatosis, and ataxia telangiectasia are well-recognized conditions associated with ALL. In this report, we describe novel association of T-cell ALL (T-ALL) with tuberous sclerosis (TS), also known as tuberous sclerosis complex (TSC). TSC is autosomal dominant neurocutaneous syndrome characterized by formation of benign hamartoma in various tissues including brain, heart, and kidneys. It is caused by mutations in tumor suppressor gene, either TSC1 or TSC2.

Case Report

A 2-year-old girl presented with 2-week history of breathlessness, fever, and generalized swellings around neck and...
axilla. On examination, child had dysmorphic facies, microcephaly, and found to have multiple hypomelanic macules (>3, > 5 mm in diameter) and shagreen patch (►Fig. 1), fulfilling two major criteria for diagnosis of TSC. The clinical diagnostic criteria for diagnosis of TSC is shown in ►Table 1. She also had cervical lymph node enlargement and moderate hepatosplenomegaly.

On admission, laboratory investigations showed hemoglobin of 8.5 g/dL, platelet count of 9,000 cells/mm³, and white blood cells of 130,000 cells/mm³. Peripheral smear revealed a normocytic hypochromic anemia with 94% lymphocytes, CD4—86.3%, CD7—84%, CD8—98.1%, CD117—86.3%, CD7—84%, CD8—4.0%, CD5—86.3%, CD7—84%, CD8—47.9%, TCRab—0.1%, and TCRgd—78.5% and precursor markers showing CD34—23.8%, CD117—38.5%, TdT—12.3, and CD99—15.5% confirmed the diagnosis.

Fig. 1 Hypopigmented macules and shagreen patch on the back of patient.

Table 1 Clinical diagnostic criteria for TSC

<table>
<thead>
<tr>
<th>Major features</th>
<th>Minor features</th>
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<tr>
<td>Hypomelanotic macules (≥3, at least 5-mm diameter)</td>
<td>“Confetti” skin lesions</td>
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<tr>
<td>Angiofibromas (≥3) or fibrous cephalic plaque</td>
<td>Dental enamel pits (&gt;3)</td>
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<tr>
<td>Ungual fibromas (≥2)</td>
<td>Intraoral fibromas (≥2)</td>
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<tr>
<td>Shagreen patch</td>
<td>Retinal achromic patch</td>
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<tr>
<td>Multiple retinal hamartomas</td>
<td>Multiple renal cysts</td>
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<tr>
<td>Cortical dysplasias^</td>
<td>Nonrenal hamartomas</td>
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<tr>
<td>Subependymal nodules</td>
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<tr>
<td>Subependymal giant cell astrocytoma</td>
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<tr>
<td>Cardiac rhabdomyoma</td>
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<tr>
<td>Lymphangioleiomyomatosis^b</td>
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<tr>
<td>Angiomyolipomas (≥2)^b</td>
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</table>

Abbreviation: TSC, tuberous sclerosis complex.

Notes: Definite diagnosis: Two major features or one major feature with ≥2 minor features. Possible diagnosis: Either one major feature or ≥2 minor features.

^ Includes tubers and cerebral white matter radial migration lines.

^b A combination of the two major clinical features (lymphangioleiomyomatosis [LAM] and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.
As discussed earlier, the association of TSC with tumors is well known, but hematopoietic malignancies are not commonly known to be associated with it. To our knowledge, this is the first case of association between TSC and a T-ALL. Occurrence of ALL in TSC by coincidence is less likely, as both the disorders are very rare. Alternatively, it is conceivable that there is a causal relationship between TSC and T-ALL. Possibly, somatic mutation in TSC1 or TSC2 genes in hematopoietic stem cells may provide second hit, with germline mutation being first hit, to trigger leukemogenesis. Indeed, PI3K–Akt–mTOR signaling pathway is frequently upregulated in T-ALL and is associated with poor prognosis. Similarly, Chiang et al have demonstrated how common β-chain-associated protein facilitates suppression of TSC2 with subsequent Rheb–mTORC1 activation in T-ALL cell line. Moreover, Xu et al found that hypermethylation of TSC2 promoters led to downregulation of expression of TSC2 in acute leukemia blasts. This emphasizes role of hamartin and tuberin and mTOR pathway in leukemogenesis and as possible therapeutic targets. Indeed, preclinical studies have shown promising results of activity of mTOR inhibitors in T-ALL. Nonetheless, this needs further exploration with the ultimate goal of its clinical application. We could not study PI3K–Akt–mTOR signaling pathway functional studies in our patient. However, we believe that our observation of this novel and rare association of ALL is of relevance, particularly to stimulate further research.

**Conclusion**

One should have a high index of suspicion for malignancies in cancer predisposing syndromes. We underline the rare development of hematological malignancy in TSC.

**Declaration of Patient Consent**

The authors certify that they have obtained all appropriate patient consent forms.

**Conflict of Interest**

None declared.

**References**


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**Fig. 2** Role of TSC1 and TSC2 in mechanistic target of rapamycin (mTOR) pathway and tumorigenesis.
16 Kim LC, Cook RS, Chen J, mTORC1 and mTORC2 in cancer and the tumor microenvironment. Oncogene 2017;36(16):2191–2201