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CASE SERIES

Acute leukemias in a Background of Neurocutaneous Syndromes

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Abstract

Background: Neurocutaneous syndromes are a group of hereditary disorders affecting the skin and the central nervous system. The association between neurocutaneous syndromes and acute leukemias is rare, and very few cases have been described in the literature. **Methods:** Here we present three cases: two cases of acute lymphoblastic leukemia associated with sturge-weber syndrome and one case of acute myeloid leukemia in a known case of tuberous sclerosis. **Results:** The association between NCS and acute leukemia denotes a poor prognosis, as evident by the fact that two out of three patients in the present triology series expired. **Conclusions:** One should have a high index of suspicion for malignancies in cancer-predisposing syndromes to help in early diagnosis and treatment. Drugs affecting the mTOR pathway could be of possible benefit to these group of patients along with prophylactic anticonvulsant therapy for seizure prevention.

Keywords: Neurocutaneous syndromes- hereditary- acute leukemia- sturge-weber- tuberous sclerosis

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Introduction

Neurocutaneous syndromes (NCS) are a group of genetic disorders involving the skin and central nervous system characterised by dysplasia in various tissues and the formation of tumours in various organs [1]. Also referred to as phakomatoses, they include neurofibromatosis, tuberous sclerosis, von-hippel-lindau disease, and sturge-weber syndrome. Associations between acute leukaemias and li Fraumeni syndrome, down syndrome, neurofibromatosis type 1, fanconi's anemia, ataxia-telangiectasia, klinefelter syndrome, and diamond blackfan anemia are well established [2, 3]. But the association between sturge-weber syndrome and tuberous sclerosis with acute leukemias is rare. Tuberous sclerosis (TS), also known as Bourneville–Pringle disease, is a rare autosomal dominant neurocutaneous syndrome caused by mutations in the TSC1 (tuberin) and TSC2 (hamartin) genes with a prevalence of 1 in 6000-12000 [4]. It is characterised by the triad of seizures, mental retardation, and cutaneous angiofibromas [5]. Sturge weber syndrome (SWS), also known as encephalotrigeminal angiomatosis, is caused by a mosaic somatic mutation in GNAQ involving the skin and central nervous system, occasionally with ophthalmologic manifestations. Typically, it presents as a facial port wine stain with an overall prevalence of 1 in 20,000-50,000 [6]. SWS is subclassified into three types: type 1, the classic form that includes facial and leptomeningeal angiomatosis with or without glaucoma; type 2, facial angioma and possible glaucoma, without intracranial involvement; and type 3, leptomeningeal angioma but no facial angioma or ocular manifestation [7].

Case presentations

Here we present three cases: two cases of acute lymphoblastic leukemia associated with sturge-weber syndrome and one case of acute myeloid leukemia in a known case of tuberous sclerosis.

Case 1

A 13-year-old girl with SWS type 1 and no previous seizure history presented with progressive pallor, requiring blood transfusions for the last two months. On examination, generalised lymphadenopathy was present. A complete hemogram showed haemoglobin 5 g/dl, a total leukocyte count of 18,500/cu mm (absolute neutrophil count 3,000/cu mm and 40% medium-sized blasts with condensed chromatin and scanty cytoplasm), and platelet count of 40,000/cu mm. Immunophenotyping (IPT) from

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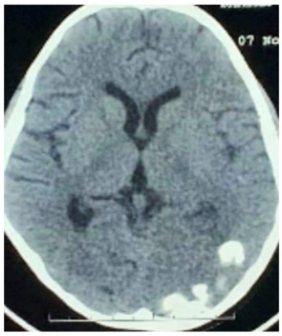

Figure 1. 13-years-old Girl with SWS Type 1 with CT Head Showing Linear Gyriform Areas of Calcification along the Cortical Sulci of Left Occipito-parietal Lobe

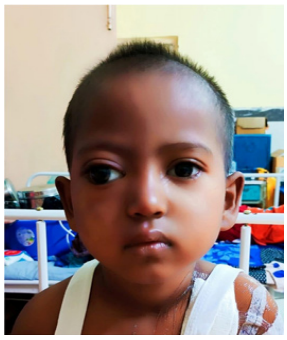

Figure 2. Six-years-old Girl with SWS Type 2 Showing Classical Port Wine Stain with Right Eye Glaucoma

peripheral blood revealed gated cells positive for CD34, CD45, CD79a, CD19, CD20, and CD22 suggestive of B cell precursor- acute lymphoblastic leukemia (BCP-ALL). The patient was started on Berlin-Frankfurt-Munich (BFM) 2002 protocol with prophylactic levetiracetam therapy. Her day 8 poor prednisolone response, cns status 2, and day 33 bone marrow in morphological remission. She received high risk block as consolidation. During the second block, she developed her first seizure episode. The CT head revealed linear gyriform areas of calcification along the cortical sulci of the left occipito-parietal lobe (Figure 1). A neuromedicine consultation was taken, and tablet phenytoin, along with lacosamide, was added to the therapy. The rest of the consolidation phase was uneventful, but after 7 months of maintenance therapy, the patient developed repeated seizure episodes and expired 1 month ago.

Case 2

A six-year-old girl with SWS type 2 and no previous seizure history presented with intermittent fever and progressive pallor, requiring blood transfusions for the last 1 month. History of right eye glaucoma was operated on two years ago. On examination, a classical port wine stain (Figure 2) along with generalised lymphadenopathy and mild splenomegaly were present. A complete hemogram showed haemoglobin 8 g/dl, a total leukocyte count of 8,500/cu mm (absolute neutrophil count 1,000/cu mm and 50% medium sized blasts with condensed chromatin and scanty cytoplasm) and platelet count of 90,000/cu mm. IPT from peripheral blood revealed gated cells positive for CD34, CD45, CD79a, CD19, and CD22 suggestive of BCP-ALL. The patient was started on BFM 2002 protocol with prophylactic levetiracetam therapy. Her day 8 prednisolone response was good, cns status 1 and day 33 bone marrow in morphological remission. The patient is now in the consolidation phase, awaiting the third high-dose methotrexate, and is doing well.

Case 3

A nine-year old boy with TS with a previous history of infantile seizures presented with progressive pallor, requiring blood transfusions for the last month. The patient was on oral levetiracetam therapy. On examination, hypopigmented macules and ungula fibromas were present [Figure 3A]. A complete hemogram showed haemoglobin 4.2 g/dl, a total leukocyte count of 23,700/cu mm (an absolute neutrophil count 6,000/cu mm and 50% large-sized blasts with prominent nucleoli, condensed chromatin, and moderate cytoplasm; a few blasts had auer rods), and a platelet count of 10,000/cu mm. IPT from peripheral blood revealed gated cells positive for CD34, CD45, MPO, CD13, CD117, and CD22 suggestive of acute myeloid leukemia (AML). Cytogenetics was 46 XY, and molecular markers were negative. On reviewing previous reports, CT head showed characteristic subependymal nodules, and MRI brain revealed cortical tubers [Figure 3B, 3C]. The patient was started on a cytarabine and daunorubicin induction protocol along with oral levetiracetam. Unfortunately, the patient succumbed to his illness on day 35 of therapy due to febrile neutropenia.

Discussion

NCS are rare diseases, with an incidence below 1:2,000 individuals in the general population. The association between NCS and acute leukemia is rare. To our knowledge, this is the third case report showing the association between SWS and ALL, the latest by Brodowska B et al [8].

In the case of tuberous sclerosis, the association is even rarer. In a case report published by Sampagar et al., the association between T-ALL and TS was shown [9]. To our knowledge, this is the first case of an association between TS and AML. The TSC complex is a negative

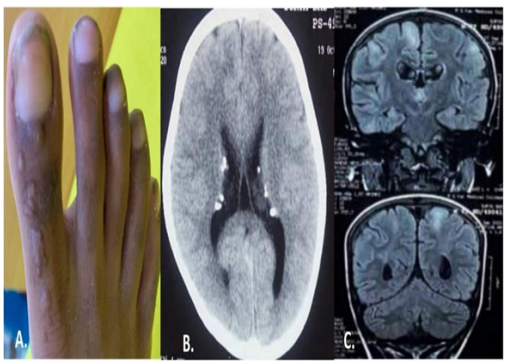

Figure 3. Nine-years-old Boy with TS Showing A. Ungual fibromas, B. CT Head showing characteristic subependymal nodules, C. MRI Brain showing multiple cortical tubers

regulator of the mTOR pathway that activates cell cycle progression. Hence, drugs affecting the mTOR pathway could be of possible benefit to this group of patients with acute leukemia.

The association between NCS and acute leukemia denotes a poor prognosis, as evident by the fact that two out of three patients in our triology series expired.

In conclusion, the association between acute leukaemias and neurocutaneous syndromes is rare. We demonstrated the novel association between ALL in the background of SWS and AML in the case of TS. One should have a high index of suspension for malignancies in cancer-predisposing syndromes. Prophylactic anticonvulsant therapy is a must for seizure prevention.

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Conflicts of interest

The authors declare no conflict of interest.

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