

neurofibromatosis and ALL.

A six year-old male child born of a nonconsanguineous marriage was referred to the Department of Dermatology from the Pediatric Oncology Unit for multiple hyperpigmented lesions on the trunk and thighs. These were present since birth and slowly progressive in nature. The child had initially presented to the Pediatric Oncology Unit about one and a half years ago with a clinical history and features suggestive of acute leukemia. Bone marrow cytology confirmed the diagnosis of acute lymphocytic leukemia (ALL-L1 type). He was started on chemotherapy and presented to us at the 14<sup>th</sup> month of chemotherapy while in remission. There was no family history suggestive of NF or any other form of cancer.

A dermatological examination revealed multiple café-au-lait macules (> 6) on the abdomen, back and thighs having sharp serrated margins and geographic borders. The lesions were not uniform in shape and their dimensions ranged from 3 x 3 cm (approx.) to 15 x 10 cm (approx.). Pigmentation over these café-au-lait macules was not homogenous with 0.4-0.9 cm-sized, darker, hyperpigmented macules present within larger, lighter macules. Similar smaller hyperpigmented macules were also present on the trunk. Freckling was present in the inguinal region. No neurofibroma was evident. Child had IAP (Indian Academy of Pediatrics) Grade III malnutrition and anemia (Hb = 7.8 g%). The platelet count, leukocyte count, urine microscopy and serum electrolytes were within normal limits. Spinal and chest radiology, cranial computed tomography (CT) scan, electroencephalogram (EEG), audiogram and slit lamp examination revealed no abnormalities. The intelligence quotient was normal. With this history, clinical examination and investigations, a diagnosis of sporadic neurofibromatosis, type-1 (NF-1) with ALL-L1 (in remission) was made.

Children usually do not yield enough results to meet NF-1 criteria and cutaneous neurofibromas often do not appear until late childhood or puberty.<sup>[2]</sup> NF-1 patients have an increased risk of developing second malignancy, viz. leukemia, rhabdomyosarcoma, optic glioma, brain tumors and they may develop neuroectodermal malignancies later in life.<sup>[1]</sup> Among leukemias, NF-1 is predominantly associated with nonlymphocytic leukemia.<sup>[1]</sup> Consequently, childhood ALL has been rarely reported in association with NF-1. Interestingly, as seen in a few elaborate studies reported in literature, sporadic NF-1 has shown a higher incidence in ALL cases than in nonlymphocytic leukemia cases.<sup>[1,3]</sup> Miller *et al.* reported that the ratio of ALL to nonlymphocytic leukemia patients was 5:3 among sporadic NF-1 and 4:15 among patients with familial NF-1.<sup>[3]</sup>

## Acute lymphocytic leukemia in sporadic neurofibromatosis

Sir,

Acute lymphocytic leukemia (ALL) is the most common pediatric malignancy accounting for 3/4<sup>th</sup> of all freshly diagnosed leukemias in childhood.<sup>[1]</sup> Neurofibromatosis (NF) is a common autosomal disorder with markedly variable expressivity. Attention is drawn to the fact that although NF-1 cases have a high risk of developing nonlymphocytic leukemia, sporadic NF cases have a greater chance of developing ALL. We report a rare association of sporadic

NF-1 develops as a result of mutations in the *NF1* gene which is located on 17q 11.2.<sup>[1]</sup> The product of this gene interacts with the ras p21 protein and may regulate *ras* activity. Mutations of the *ras* gene have been reported in some myelogenous leukemias (juvenile chronic myelogenous leukemia (CML) and myelodysplastic syndrome) but they are relatively less common in ALL.<sup>[4]</sup> This may account for a more consistent association observed between NF-1 and nonlymphoblastic leukemias. But at the same time, this explanation is unable to account for the relatively higher cases of ALL occurring in patients with sporadic NF-1. There is a strong possibility of the additional involvement of some other mechanism in patients having sporadic NF-1 and ALL. It has been suggested that it is the general lack of MMR from conception that causes the occurrence of sporadic NF-1 and hematological malignancy in these rare MMR-deficient individuals.<sup>[5]</sup> Individuals homozygous for mutations in either of the mis-match repair (MMR) genes, *MLH1* and *MSH2*, developed hematological malignancies and / or NF-1 at an early age just like our patient.<sup>[6]</sup>

The relatively young age of the parents or an occult malignancy may explain the lack of observed cancer in our pedigree at the time of ascertainment. It may be possible that a malignancy may be reported in the future. The family has been advised to undergo regular follow-up for the early detection of any malignancy. In spite of the non consanguinity, an ancestral heterozygous *MSH2* mutation cannot be ruled out in the parents since they belong to same ethnic, racial and geographical background. To the best of our knowledge, this is the first time such an association is being reported in India. The purpose of reporting this case is to draw attention to a possible association between the pathogenesis of ALL and sporadic NF-1. Patients and the families of NF-1 patients must undergo a close, long-term follow-up.

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