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Title	Subcutaneous panniculitis-like T-cell lymphoma with homozygous germline HAVCR2 mutation: a case report
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Abstract

A 30-year-old man was admitted for on-and-off fever for 2 weeks. He also complained of painful nodules over trunk and limbs for 4 months. He had a previous history of painful nodules occurred for months and subsided spontaneously in his teenage but he didn't attend medical attention. On physical examination, there were multiple tender erythematous nodular swellings over chest wall and bilateral thighs with no lymphadenopathy. Ultrasound abdomen showed hepatosplenomegaly. Complete blood count showed mild anaemia (hemoglobin 11.0 g/dL). He had mildly elevated ALT of 120 U/L, markedly elevated lactate dehydrogenase of 1194 U/L and ferritin of 26625 pmol/L. He had worsening anaemia and neutropenia and bone marrow examination showed some haemophagocytosis with no obvious marrow infiltration. A skin biopsy was performed and showed subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Further Sanger sequencing targeting HAVCR2 gene exon 2 was performed on the bone marrow aspirate specimen. Homozygous p.Y82C mutations, (NM_032782.5:c.245A>G), was detected. Confirmatory germline testing on hair follicles was not performed since there was no lymphomatous involvement in bone marrow. The patient was given cyclosporin A 100 mg BD PO and prednisolone 30 mg BD PO. The skin lesions gradually improve and steroid was tailed down gradually. After 3 months of treatment, the skin lesions were completely resolved. His ferritin returned to normal (588 pmol/L) and LDH is slightly elevated at 239 U/L.

The Hepatitis A Virus-Cellular Receptor 2 (HAVCR2) gene encodes the T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), a critical negative regulator acting as a negative checkpoint in innate immune and inflammatory responses. Recent studies have identified germline homozygous or compound heterozygous mutations on HAVCR2 gene in 59-85% of SPTCL patients including familial and sporadic cases, and are associated with a younger age of onset of disease. About 20% of the cases also show haemophagocytic lymphohistiocytosis (HLH). The currently reported germline HAVCR2 mutations associated with SPTCL were p.Y82C, p.I97M, and p.T101I mutations, with p.Y82C being the most frequently reported mutation as seen in this patient. The reported minor allele frequency of p.Y82C in South Asians was 2.1×10^{-2}. Remarkable enrichment of the p.Y82C homozygote was also reported in SPTCL (odds ratio 1.2×10^{5}), suggesting a strong association between HAVCR2 (TIM-3) germline mutations and familial or sporadic SPTCL and/or HLH.

The presence of HLH in SPTCL is associated with adverse prognosis (5-year survival of <50% in cases with HLH compared with 90% in cases without HLH). There is no standard treatment approach for SPTCL. Common treatment options would include immunosuppressive therapy (steroid plus cyclosporin A) and chemotherapy (CHOP +/- E followed by haematopoietic stem cell transplantation). Ruxolitinib has also recently been reported to be efficacious in paediatric cases of SPTCL-HLH with germline homozygous mutation of HAVCR2 (p.Y82C).

Reference:

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