First reported case of alveolar soft part sarcoma in constitutional mismatch repair deficiency syndrome tumor spectrum - diagnosed in one of the siblings with constitutional mismatch repair deficiency

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Dear Editor,

DNA mismatch repair (MMR) is a system for recognizing and repairing errors, which occur during DNA replication and recombination. Biallelic deleterious germline mutations in MMR genes (MLH1, MSH2, MSH6, and PMS2) lead to constitutional MMR deficiency syndrome (CMMR-D).[1]

We are reporting two cases of CMMR-D in siblings of a family, who developed acute lymphoblastic leukemia (ALL) with glioblastoma multiforme and ALL with alveolar soft part sarcoma (ASPS) (first case in CMMR-D spectrum) respectively.[2]

Sibling 1

An 8-year-old girl presented in 2006 with fever, petechiae, and epistaxis for 2 weeks. Complete blood count (CBC), immunohistochemistry (IHC), and bone marrow (BM) examination revealed T-ALL.

She was treated with MCP-841 chemotherapy and whole brain irradiation (18 Gy in 10 fractions). Then, remission was achieved.

After 4 years, she was again admitted with left hemiparesis in 2013, and magnetic resonance imaging showed well-defined heterogeneously enhancing solid cystic space occupying lesion (SOL) involving right parietal lobe [Figure 1a].

Near total excision of SOL with parietal craniotomy was then done.

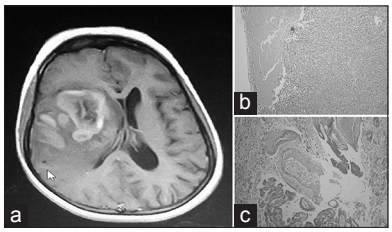

Figure 1: (a) Magnetic resonance imaging showed well-defined heterogeneously enhancing solid cystic space occupying lesion involving right parietal lobe. (b and c) Histologically, it was a cellular tumor composed of proliferating astrocytes with nuclear pleomorphism

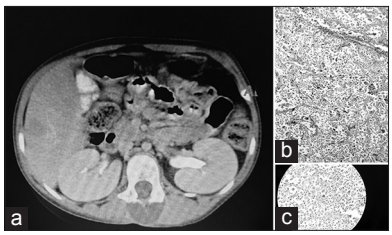

Figure 2: (a) Computed tomography abdomen showed heterogeneously enhancing soft tissue lesion in paravertebral location on the left side. (b and c) Histologically, high-grade malignant tumor with polygonal cells arranged in alveolar pattern amidst areas of necrosis

Histologically, it was a cellular tumor composed of proliferating astrocytes with nuclear pleomorphism [Figure 1b and c].

There were multinucleated tumor giant cells along with areas of necrosis and vascular endothelial proliferation. There was mitosis with Ki-67 index - 35%.

A diagnosis of glioblastoma multiforme was made.

Sibling 2

A 6-year-old boy, [brother of Sibling 1-girl] presented in 2012 and his CBC, IHC, and BM findings confirmed it to be the case of T-ALL.

Then, he was given the treatment for the same with BFM-90 protocol, which was completed in 2013 and remission was achieved.

After 6 months of disease-free survival, in 2014, he presented again, and computed tomography abdomen showed heterogeneously enhancing soft tissue lesion in paravertebral location on the left side [Figure 2a] at that time.

There was involvement of adjacent body of D9, D10 vertebrae, and posterior end of the 9th rib on the left side and possibility of metastasis.

Then, the patient was referred to the Tata Memorial Hospital (TMH), Mumbai, where he again developed recurrence of paraspinal mass and underwent laminectomy at TMH for the same.

Histologically, high-grade malignant tumor with polygonal cells arranged in alveolar pattern amidst areas of necrosis [Figure 2b and c] was seen.

Periodic acid-Schiff stain with diastase highlights intracytoplasmic granules and crystals.

On IHC, the tumor cells were positive for transcription factor E3 and integrase interactor 1 (INI1).

On IHC, tumor cells were negative for epithelial membrane antigen, synaptophysin, CD56, S-100 P, smooth muscle actin, human melanoma, black 45, desmin, glial fibrillary acidic protein, CD34, and PAX-8.

On the basis of these findings, final diagnosis of ASPS was made.

PMS2 genetic study of Sibling 2 is described as below:

A homozygous deletion (chr7:6026910; delC) was detected in exon 11 of the PMS2 gene in this subject. This mutation results in a frame shift mutation. (c. 1486delC at codon 496) - (p.His496ThrfsTer99) leading to premature termination of the protein translated from PMS2 gene, 99 amino acids after the position of frame shift.

Discussion

CMMR-D spectrum includes varieties of tumors such as hematologic malignancies (31%), (which include mainly T-cell non-Hodgkin lymphoma and acute leukemia) and brain tumors (53%), (most common among brain tumors are high-grade glioma, followed by primitive neuroectodermal tumors and medulloblastoma).

Around 146 patients of CMMR-D in 91 families were identified in the world literature and the most frequent defects were PMS2 mutations in approximately 60% patients.[3]

Based on the analysis of genetic report of Sibling 2 showing homozygous deletion in PMS2 gene after the position of frame shift, we confirmed the Sibling 2 as a case of CMMR-D.[3]

In the Sibling 1, genetic test is not possible due to death of the patient at the age of 16 years.

Both siblings of one family score >3 (Sibling 1-10 and Sibling 2-8) on diagnostic criteria suggested by European Consortium "Care for CMMRD." (C4CMMRD),[2] described in Supporting File 1.[2]

Hence, after scoring both these siblings as above, they become highly probable cases of CMMR-D.

As described earlier, we are confirming Sibling 2, as the first reported case of ASPS, among CMMR-D spectrum.

Conclusion

In a case of CMMR-D, it was suggested to analyze IHC for the expression of MMR proteins. Then, for further confirmation, germline mutational analysis of the MMR genes should be considered after counseling their parents.

As very few hematologists/oncologists are aware of the CMMR-D, it should be kept in mind as a possibility while coming across relevant cases.

The diagnosis of CMMR-D should be confirmed by gene-specific mutation analysis. Mutation analysis will facilitate identification and surveillance of heterozygous and homozygous individuals in family and help in prenatal or preimplantation genetic diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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Supporting File 1

Indication criteria for CMMRD testing in cancer patients[2]	≥3 points
Sibling 1	
WHO grade III or IV glioma at age <25 years	2 points
NHL of T-cell lineage or sPNET at age <18 years	2 points
Any malignancy at age <18 years	1 point + 1 point
A sibling with carcinoma from the LS spectrum, high-grade glioma, sPNET or NHL	2 points
A sibling with any type of childhood malignancy	1 point
Consanguineous parents	1 point
Total	10 points
Sibling 2	
NHL of T-cell lineage or sPNET at age <18 years	2 points
Any malignancy at age <18 years	1 point + 1 point
A sibling with carcinoma from the LS spectrum, high-grade glioma, sPNET or NHL	2 points
A sibling with any type of childhood malignancy	1 point
Consanguineous parents	1 point
Total	8 points

NHL=Non-Hodgkin's lymphomas, sPNET=Supratentorial primitive neuroectodermal tumors, LS=Lynch Syndrome