Secondary Malignancies Developing After Acute Lymphoblastic Leukemia And Its Treatment With Constitutional Mismatch Repair Deficiency Syndrome In Siblings

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Abstract: Background & Objectives: Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy, with an annual rate of 3 to 4 cases per 1,00,000 children. ALL patients are treated with chemotherapeutic agents and cranial irradiation. Long-term sequelae of treatment are impaired intellectual and psychomotor functioning, neuroendocrine abnormalitites, impaired reproductive capacity, cardiotoxicity and second malignant neoplasms are being reported with increased frequency in the survivors. Among second neoplasms observed after treatment of ALL, central nervous system (CNS) tumors in patients treated with cranial irradiation are the most common. Others are Lymphoma, Acute Myeloid Leukemia (AML) and Thyroid Cancer. Methodology & Results: We are reporting four cases ,who developed ALL at the age of 8,6,4 and 25 years respectively(among that case 1 & case 2 are siblings) and were treated with chemotherapy and cranial irradiation. They developed Astrocytoma Grade-4 , Alveolar Soft-Part Sarcoma(ASPS) , Anaplastic Large Cell Medulloblastoma & Ewing's Sarcoma at, 12 , 15, 8, 12 & 26 years of age respectively. Conclusion: Oncologists should make sure about the radiation doses before starting treatment and they should keep CMMR-D as a possibility in pediatric patients with siblings having h/o malignancy. [Modi M NJIRM 2016; 7(2):44-51]

Key Words: Alveolar Soft part Sarcoma, Constitutional mismatch repair deficiency syndrome, Acute Lymphoblastic Leukemia, Neural tumor.

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Introduction: Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy, with an annual rate of 3 to 4 cases per 1,00,000 children. ALL patients are treated with chemotherapeutic agents and cranial irradiation. Long-term sequelae of treatment, such as impaired intellectual and psychomotor functioning, neuroendocrine abnormalitites, impaired reproductive capacity, cardiotoxicity and second malignant neoplasms are being reported with increased frequency in the survivors.

For survivors of childhood ALL, the estimated actual risk of developing a second neoplasm has been reported to be 2.5% at 15 years from diagnosis. Among second neoplasms observed after treatment of ALL, central nervous system (CNS) tumors in patients treated with cranial irradiation are the most common. Other commonly reported second neoplasms in this population include Lymphoma, Acute Myeloid Leukemia (AML) and Thyroid Cancer.[1,2,3]

DNA mismatch repair is a system for recognizing and repairing deletion,insertion and mis-incorporation of bases which can arise during DNA replication, recombination and repairing DNA damage.While heterozygous germline mutations in *MLH1, MSH2, MSH6 AND PMS2* (mismatch repair(MMR) genes)cause lynch syndrome(LS) associated hereditary non-polyposis colorectal cancer (HNPCC),biallelic deleterious germline mutations in MMR genes leading to Constitutional mismatch repair deficiency syndrome.(CMMR-D)[4] Diagnosis is major problem with CMMR-D cases due to lack of awareness among pediatric hematologists/oncologists.

We are reporting four cases ,who developed ALL at the age of 8,6,4 and 25 years respectively(among that case 1 & case 2 are siblings with CMMR-D) and were treated with chemotherapy and cranial irradiation. They developed Astrocytoma Grade-4 , Alveolar Soft-Part Sarcoma(ASPS) , Anaplastic Large Cell Medulloblastoma & Ewing's Sarcoma at, 12 , 15, 8, 12 & 26 years of age respectively.

Based on the current knowledge on the tumor spectrum case 2 will be the first case of ASPS reported in CMMR-D[5] and first ASPS case developing after ALL.

Material and Methods: We have taken an Informed consent from the relevant families and patients for the publication of this article and we also showed them this manuscript to be published. The two siblings of a family –Case1-Sibling 1 presented at 8 years and expired at the age: 15 years , Sex:female, Ethnicity:

Indian, Case 2-Sibling 2: Age: 6 years , Sex: male, Ethnicity: Indian. Case 3: Age :4 years, Sex: Male, Ethnicity: Indian. Case 4: Age :25 years, Sex: Male, Ethnicity: Indian We used biopsy, Immunohistochemistry(IHC), fluid cytology, bone marrow(BM) aspirations for the patients' management at our institution Gujarat cancer & research institute (GCRI). Case 2(Sibling 2) was referred to Tata Memorial Hospital(TMH),Mumbai for further management.

Results:

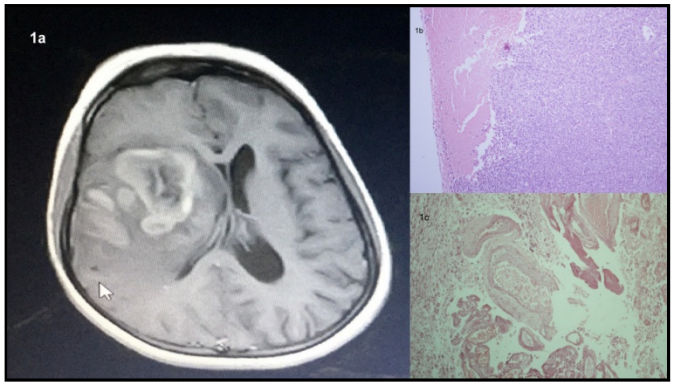
Case 1(Sibling 1)

A 8 year old girl was presented in January 2006 for the c/o fever,petechie and epistaxis for 2 weeks with no past h/o. CBC (Complete Blood Count),IHC and BM examination revealed T-ALL.

She was treated with MCP-841 chemotherapy along with 12 doses of intrathecal methotrexate and whole brain irradiation (18 Gy in 10 Fractions). Her chemotherapy was completed in March,2008. Remission was also achieved.

After 4 years of disease free survival she was again admitted for the c/o left hemiparesis and left facial palsy in 2013. MRI (Figure-1a)showed well defined heterogeneously enhancing solid cystic space occupying lesion(SOL) involving right parietal lobe. Near total excision of SOL with parietal craniotomy was done.

Figure 1:



Histologically,(Figure-1b,1c) it was a cellular tumor composed of proliferating astrocytes with nuclear pleomorphism. There was multinucleated tumor giant cells along with areas of necrosis and vascular endothelial proliferation. There was also mitosis and Ki-67 index-35%.

A diagnosis of Astrocytoma Grade-4 was made.

At post operative 2 weeks, temozolamide 75 mg/m^2/day was administered with 60 Gy of cranial irradiation to whole brain in 30 fractions and she was on temozolamide 250 mg/day for following months.
But after that patient died at the age of 16 years. So,further workup including genetic study was not possible.

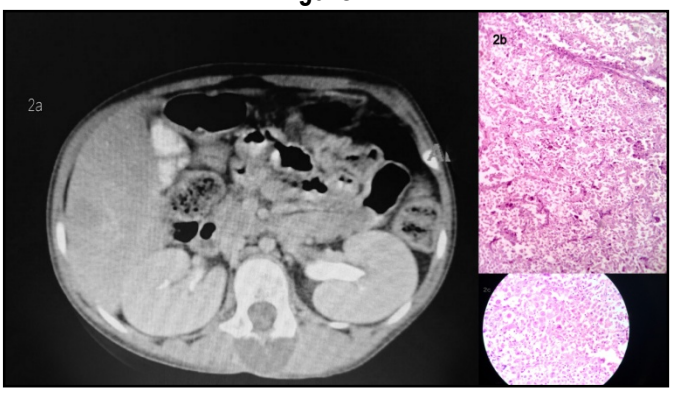
Case 2(Sibling 2)

A 6 year old boy brother of sibling 1-girl(having ALL with Astrocytoma G-4) presented with c/o high grade fever,sore throat, neck swelling for 2 weeks in December,2012. After having admitted to GCRI, his CBC,IHC and BM finding confirmed it to be T-ALL.

So he was started the treatment for the same with BFM-90 protocol, after that 9 blocks of high dose mehotrexate and then 12 Gy of cranial irradiation in 10 fractions is given, which was completed in september,2013. Remission was achieved.

After 6 months of disease free survival, in February,2014 he had c/o of severe backache. On p/e he was found out to have paraspinal mass in the back.
CT abdomen showed heterogeneously enhancing soft tissue lesion in paravertebral location on left side with involvement of adjacent body of D 9 , D 10 vertebrae & posterior end of 9th rib on left side . Multiple lesions on both lobes of liver. p/o metastasis.

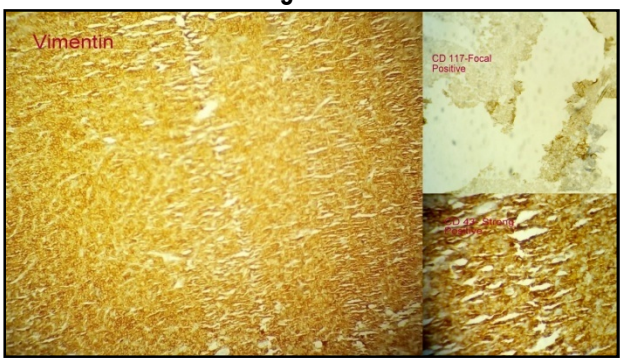
Figure 2:



Complete resection of tumor and Laminectomy performed for paraspinal mass respectively in April,2014 and May,2014 in addition to two cycles of Cobalt Radiation. Based on morphology diagnosis of malignant ganglionic cell tumor was given. Biopsy

report showed proliferation of atypical ganglionic cells with mitosis with no evident necrosis. In November,2014 he again developed recurrence of paraspinal mass and underwent laminectomy at Gujarat Cancer & Research Institute, Ahmeabad. Then the patient was referred to TMH, Mumbai for further workup and treatment.

Figure 3:



Histologically, (Figure-3a,3b) High grade malignant tumor with polygonal cells arranged in alveolar pattern amidst areas of necrosis. PAS with diastase highlights intracytoplasmic granules and crystals.

IHC: (Figure-3c), the tumor cells were positive for TFE 3 ,While negative for EMA, synaptophysin, CD 56, S 100-P, SMA, HMB 45, Desmin, GFAP, CD 34 & PAX 8. INI 1 is retained.

On the basis of these finding final diagnosis ALVEOLAR SOFT PART SARCOMA was made.

As both children in one family were having ALL with secondary malignancy, possible genetic etiology in this family was suspected. So, *PMS2* genetic study of sibling 2 was done and report 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 frameshift (p.His496ThrfsTer99) at codon 496 leading to premature termination of the protein translated from *PMS2* gene , 99 aminoacids after the position of frameshift.

Then he had 3 cycles of Palliative Radiotherapy from February,2015 at Tata Memorial Hospital, Mumbai. Currently, he is on Tab Everolimus 5 mg OD for 3 weeks with 1 week of gap in 4 weeks with regular follow-up monthly at TMH,Mumbai.

Both siblings score (>3): sibling 1-9 points and sibling 2-7 points

As described in discussion on diagnostic criteria suggested by European Consortium 'Care for CMMRD'. (C4CMMRD)[2]

Case 3

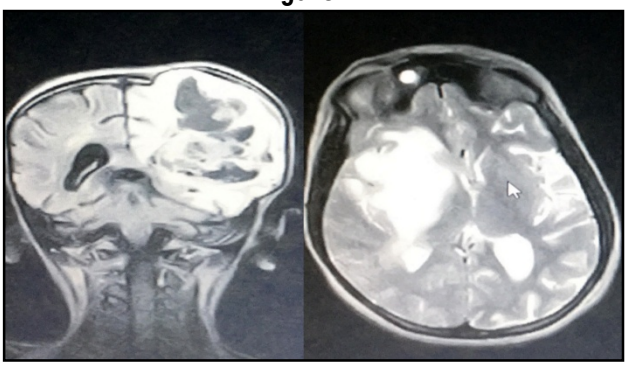
A four year old boy was admitted to GCRI who presented with c/o high grade fever for two weeks in November 2005. There was no h/o lymphadenopathy / hepatosplenomegaly / bleeding /prior similar illness/family h/o cancer/hereditary disease. His CBC & Bone Marrow Examination finding revealed ALL.

He was treated with MCP-841 chemotherapy regimen and had received 12 doses of intrathecal methotrexate and prophylactic cranial irradiation (total dose of 18 Gy in 10 Fractions) during that period. Chemotherapy was completed in 2007 & BM findings achieved complete remission.

After that he was on regular follow-up and in August,2010 he came back again with c/o high grade fever.Peripheral Smear(PS) and Bone Marrow(BM) findings also proved it to be a relapse of leukemia. He was again treated with MCP-841 chemotherapy regimen along with intrathecal methotrexate and intracranial irradiation.

After one year of disease free survival,in May,2013 he patient presented with c/o of convulsions and right hemiparesis. (MRI) of the brain showed heterogeneously enhancing lesion in left parietao-temporal region associated with mild perilesional edema. Few hemorrhagic foci were seen within lesion. Excision of space occupying lesion(SOL) & left parietal craniotomy was done.

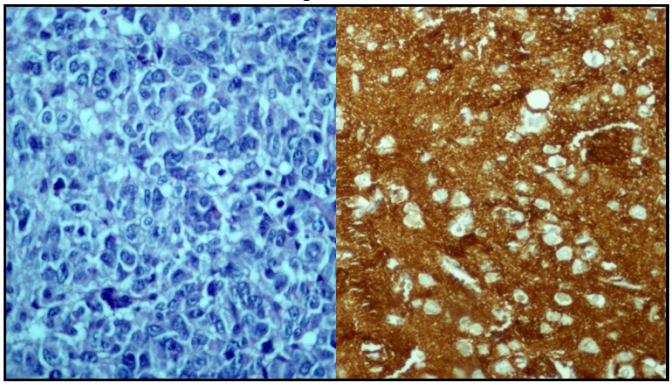
Figure 4:



Brain MRI report-Post operative status dated 5th August,2013 showed residual large mass lesion involving left parietal & occipital region and herniation of brain parenchyma. As compared to previous MRI in May,2013 there is significant increase in size of lesion. Histologically(5a), the most striking feature was sheet of small tumor cells with scanty cytoplasm and nuclei of similar sizes. Small blue round tumor cells seen.

On Immunohistochemistry (IHC),(5b) the tumor was positive for Glial Fibrillary Acidic Protien (GFAP), Actin and Vimentin and negative for AE1, EMA and Desmin. Synaptophysin and Chromogranin were focally positive. In addition to that INI 1 was positive.

Figure 5:



On the basis of these findings, diagnosis of Anaplastic Large Cell Medulloblastoma was made.

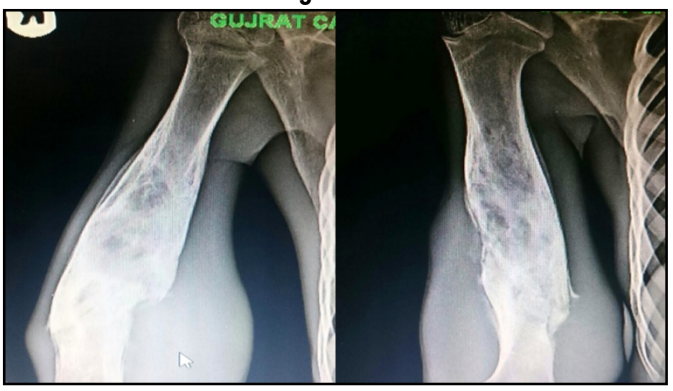
Case 5

A twenty five years man was admitted to GCRI who presented with c/o high grade fever for two weeks in September,2011. There was no h/o lymphadenopathy / hepatosplenomegaly / bleeding /prior similar illness/family h/o cancer/hereditary disease. CBC and Bone Marrow Examination finding with Immunophenotyping revealed ALL in October,2011.

He was treated with MCP-841 chemotherapy regimen (Prednisolone, Vincristine, Daunorubicin, L-asparginase, Cyclophosphamide and 6-Mercaptopurine) and had received 12 doses of intrathecal methotrexate and prophylactic cranial irradiation (total dose of 18 Gy in 10 Fractions) during that period.

After that he was on regular follow-up and in October,2012 he came back again with c/o left elbow pain while on the maintenance treatment of ALL. P/E confirmed it the mass around left elbow.

Figure 6:

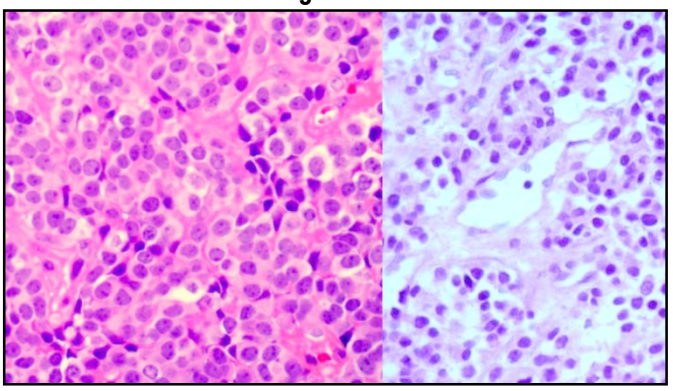


Slide Review and IHC findings also proved it to be Ewing's Sarcoma. He underwent the surgical resection of tumor.

Histologically,(7a) the tumor consists of small ,,round, blue tumor cells usually in sheets, indistinct borders, round to oval nuclei, with one to two prominent nucleoli and finely dispersed chromatin.

On IHC,(7b) the tumor was posititve for vimentin, NSE and CD 99 and negative for LCA and CD 20.

Figure 7:



The patient is on regular follow up for the management and in August,2015 his CSF fluid cytology was negative for malignant cells.

Discussion: Secondary brain tumor rarely occurs after brain radiation therapy although adverse effects such as radiation necrosis can result from the radiation itself. Recently , Sarcomas and Meningiomas have been measured to be the most frequent radiation induced brain tumors.

The causative factors for development of radiation induced Glioblastoma Multiforme is still not clearly verified. Irradiation dose, underlying disease, patient's general condition, age at irradiation , primary tissue pathology and combined chemotherapy may all contribute to the occurrence to certain extents. Concerning the radiation dose itself, there have been reports postulating that prophylactic irradiation of higher dose (usually more than 30 Gy) gives rise to higher risk of malignant brain tumor occurrence compare to that of lower dose (less than 18 Gy). On the other way. There have been counterproposals suggesting that radiation dose not always give rise to higher rate of secondary tumor development because when the radiation dosage is too high, oncogenic cells may also be eliminated.

Cahan et al. defined the radiation induced Glioblastoma Multiforme should satisfy the following criteria;

The tumor must arise within the area of previous irradiation;
A sufficient latency period (measured in years) should be present between radiation and onset of tumor growth;
There must be histopathologic difference between the primary tumor and newly developed tumor; and
The patient must be free from disease prone to carcinogenesis,such as Rechlinghausen's disease, Li-Fraumani's disease, Tuberous Sclerosis, Xerodermapigmentosum or Retinoblastoma.[6]

Many studies have been done to establish the risk of developing a second malignant neoplasm and to disentangle the role of various risk factors (i.e.,factors related to the host, initial cancer type and cancer therapies). The main risk factors for secondary malignant neoplasms in survivors of childhood cancer are radiotherapy and chemotherapy. Different tissues are not equally sensitive to radiation and host factors such as repair enzymes, rate of cell division, endocrine and immune function may be important cofactors.[7]

Although the role of radiation in carcinogenesis had been well established in humans and experimental animals, the exact mechanism of radiation induced carcinogenesis remains to be elucidated. It was demonstrated that radiation induced neoplasm appears to arise through mutagenic capacity and chromosome aberration and the mechanisms leading to neoplastic transformation involves multistage process (multi-hit kinetics) rather than a single, one-hit type of biochemical alteration.[8]

The other possible aetiological factor in the induction of patient's tumor could be combination of intrathecal methotrexate with cranial irradiation. It is known that administration of methotrexate in combination with 2000 rad or more of cranial irradiation may result in multiple necrotic areas with or without gliosis disseminated throughout the cerebral white matter (leukoencephalopathy). Statistical and clinical evidence suggests that a genetic predisposition to multiple neoplasms, synergistic action of radiotherapy and intrathecal methotrexate and prolonged exposure to methotrexate could play a role in inducing these second tumors.[9] Developing brain is more sensitive to radiation.[10,11]

CMMR-D spectrum includes varieties of tumors ranging i.e. hematologic malignancies (31%) mainly T cell non-Hodgkin lymphoma (NHL) and acute leukemia , brain tumors (53%) most common among them high grade glioma, followed by primitive neuroectodermal tumors (PNET) and medulloblastoma. Gastrointestinal tract cancers (40%) are also one of the common major malignancies in CMMR-D spectrum.[12] The spectrum of cancers observed in CMMR-D differ from other cancer syndromes as more than half of the patients develop brain tumors and prognosis is worse due to high risk of second malignancies.[12] The presence of cerebral malformations in pediatric cancer patients should alert to the possible diagnosis of CMMR-D.[13]

Around 146 patient in 91 families were identified in the world literature and the most frequent defects were *PMS2* mutations in approximately 60 % patients.[12] Reports of some other rare tumors such as neuroblastoma, Wilm tumor, ovarian neuroectodermal tumour, infantile myofibromatosis, rhabdomyosarcoma and few emryonal tumours have been documented,too.[14]

Based on the analysis of genetic report of sibling 2 showing homozygous deletion in *PMS2* gene after the position of frameshift , we can confirm the sibling 2 as case of CMMR-D.[12]

In the sibling 1 genetic test is not possible due to death of the patient at the age of 16 years. But as both siblings of one family score >3 (sibling 1 -9 & sibling 2-

7) on diagnostic criteria suggested by European Consortium 'Care for CMMRD'. (C4CMMRD)[2] , described as below on Table 1[5],

Table 1: Indication criteria for CMMRD testing in cancer patients

Indication for CMMRD testing in a cancer patient	≥3 points
Malignancies/premalignancies: one is mandatory; if more than one is present in the patient, add the points	
Carcinoma from the LS spectrum* at age <25 years	3 points
Multiple bowel adenomas at age <25 years and absence of *APC*/*MUTYH* mutation(s) or a single high-grade dysplasia adenoma at age <25 years	3 points
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	
Additional features: optional; if more than one of the following is present, add the points	
Clinical sign of NF1 and/or ≥2 hyperpigmented and/or hypopigmented skin alterations Ø>1 cm in the patient	2 points
Diagnosis of LS in a first-degree or second-degree relative	2 points
Carcinoma from LS spectrum* before the age of 60 in first-degree, second-degree, and third-degree relative	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
Multiple pilomatricomas in the patient	2 points
One pilomatricoma in the patient	1 point
Agenesis of the corpus callosum or non-therapy-induced cavernoma in the patient	1 point
Consanguineous parents	1 point
Deficiency/reduced levels of IgG2/4 and/or IgA	1 point

*Colorectal, endometrial, small bowel, ureter, renal pelvis, biliary tract, stomach, bladder carcinoma.

CMMRD, constitutional mismatch repair deficiency; LS, Lynch syndrome; NHL, non-Hodgkin's lymphomas; sPNET, supratentorial primitive neuroectodermal tumours.

Both these siblings proved to be cases of CMMR-D.

As described earlier we are suspecting this the first reported case of ASPS , among CMMR-D spectrum.

ASPS is a rare tumor that occurs mostly in young adults usually in the soft tissues of extremities . Usual presenting feature of ASPS - soft, painless, slow-growing mass that sometimes causes functional impairment. Common metastatic sites are liver (as in sibling 2), lung, bone and central nervous system. The first study done to address molecular biology and tumour cytogenetics confirmed neurgogenic origin of ASPS.[15]

The utility of an IHC assay for TFE3 protein demonstrates high specificity and sensitivity for tumors characterized by Xp11.2 translocations and resulting *TFE3* gene fusions as in ASPS.[16] Immunoreactivity for TFE3 Fusion protein in ASPS is the most accurate diagnostic feature .

To this date , this is the first case of ASPS reported in CMMR-D spectrum and first case of ASPS developing after ALL.

Conclusion: These strongly postulates that radiation itself increases the chances of the patient developing secondary malignancies. So, Oncologists should make sure about the radiation doses and protocol before starting treatment. Oncologist should also do proper counseling about the follow ups of patients , so that during follow up period they can catch secondary malignancy at early stage by proper screening with radiological and pathological diagnostic tests.As very few hematologists/oncologists are aware of the CMMR-D, CMMR-D should be kept in mind as a possibility while having positive h/o of malignancy in siblings of family, secondary malignancies in pediatric patients, hematologic malignancies, brain(neural) tumors .These features should alert the physician to look for genetic studies and CMMR-D.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 allow for informed decision-making about prenatal or pre-implantation genetic diagnosis.

References:

1. Smita Bhatia, Harland N. Sather, Olga B. Pabustan, Michael E. Trigg, Paul S. Gaynon and Leslie L. Robison. Low incidence of second neoplasm among children diagnosed with acute lymphoblastic leukemia after 1983.blood.2002; 99:4257-4264
2. Dalton VMK, Gelber RD, Li F, Donnelly MJ, Tarbell NJ, Sallan SE. Second malignancies in patients treated for childhood acute lymphoblastic leukemia. J Clin Oncol. 1998;16:2848-2853.
3. Neglia JP, Meadows AT, Robison LL, et al. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med. 1991;325:1330-1336.
4. Katharina Wimmer, Christian P. Kratz ,Constitutional mismatch repair-deficiency syndrome, Haematologica May 2010 95: 699-701; doi:10.3324/haematol.2009.021626
5. Katharina Wimmer, Christian P Kratz, Hans F A Vasen, Olivier Caron, Chrystelle Colas, Natacha Entz-Werle, Anne-Marie Gerdes, Yael Goldberg, Denisa Ilencikova, Martine Muleris, Alex Duval, Noémie Lavoine, Clara Ruiz-Ponte, Irene Slavc, Brigit Burkhardt, Laurence Brugieres, on behalf of the EU-Consortium Care for CMMRD (C4CMMRD), Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'Care for CMMRD' (C4CMMRD), Cancer genetics, J Med Genet 2014;51:6 355-365 Published Online First: 15 April 2014 doi:10.1136/jmedgenet-2014-102284
6. Daewon Joh, M.D., Bong Jin Park, M.D., Young Jin Lim, M.D. Radiation induced Glioblastoma Multiforme in a Remitted Acute Lymphocytic Leukemia patient. J Korean Neurosurg Soc 50:235-239, 2011.
7. Milena Maule, Ghislaine Scelo, Guido Pastore, Paul Brennan, Kari Hemminki, Elizabeth Tracey, Risto Sankila, Elisabete Weiderpass, Jorgen H. Olsen, Mary L. McBride, David H. Brewster, Vera Pompe-Kirn, Erich V. Kliewer, Kee Seng Chia, Jon M. Tonita, Carmen Martos, Jon G. Jonasson, Franco Merletti, Paolo Boffetta. Risk of Secondary malignant neoplasms after Childhood Leukemia and Lymphoma: An International Study. J Natl Cancer Inst. 2007;99:790-800.
8. Kirit C. Shah, Vedantam Rajshekhar. Glioblastoma Multiforme in a child with Acute Lymphoblastic Leukemia : Case report reviw of literature. Neurol. India 2004;52:375-377.
9. Muzumdar D P, Desai K, Goel A. Glioblastoma Multiforme following prophylactic cranial irradiation and intrathecal methotrexate in a child with Acute Lymphoblastic Leukemia : A case report. Neurol. India 1999;47:142-144.
10. Michelle De Padua, VijayAnand Reddy and Manohar Reddy. Cerebral atypical teratoid rhabdoid tumour arising in a child treated for acute lymphoblastic leukemia. BMJ case Rep.2009; 2009:bcr08.2008.0601.
11. Haberler C, Laggner U, CzechT, et al. Immunohistochemical analysis of INI1 protein in malignant CNS tumours: Lack of INI1 expression in atypical teratoid/rhabdoid tumours and a fraction of primitive neuroectodermal tumours without rhabdoid phenotype. Am J Surg Pathol 2006; 30 : 1462-8[PubMed: 17063089]
12. H F AVasen,Z Ghorbanoghli,F Bourdeaut, O Cabaret, O Caron, A Duval, N Entz-Werle, Y Goldberg, D Ilencikova, C P Kratz, N Lavoine, J Loeffen, F H Menko, M Muleris, G Sebille, C Colas , B Burkhardt, L Brugieres, K Wimmer, on behalf of the EU-Consortium Care for CMMR-D (C4CMMR-D) , Guidelines for surveillance of individuals with constitutional mismatch repair-deficiency proposed by the European Consortium "Care for CMMR-D" (C4CMMR-D) , Cancer genetics, J Med Genet 2014;51:283-293 doi:10.1136/jmedgenet-2013-102238
13. Baas AF, Gabbett M, Rimac M, Kansikas M, Raphael M, Nievelstein RA, Nicholls W, Offerhaus J, Bodmer D, Wernstedt A, Krabichler B, Strasser U, Nyström M, Zschocke J, Robertson SP, van Haelst MM, Wimmer K, Agenesis of the corpus callosum and gray matter heterotopia in three patients with constitutional mismatch repair deficiency syndrome.
14. C P Kratz, S Holter, J Etzler, M Lauten, A Pollett, C M Niemeyer, S Gallinger, K Wimmer, Rhabdomyosarcoma in patients with constitutional mismatch-repair-deficiency syndrome, Mutation report, . J Med Genet 2009;46:418-420 doi:10.1136/jmg.2008.064212
15. Catherine Cullinane,MA, Paul S. Thorner, M.D., Ph.D.,Mark L.Greenberg, M.D., t Yim, Kwan Ng ,B.Sc., Margarete Kumar,B.Sc., and Jeremy Squire, Ph.D.,
16. Molecular Genetic,Cytogenetic,and Immunohistochemical Characterization of Alveolar Soft-Part Sarcoma ,Implications for Cell of Origin.

Cancer (Impact Factor: 4.9). 11/1992; 70(10):2444 – 2450
17. Argani, Pedram M.D.; Lal, Priti M.D.; Hutchinson, Brian M.A.; Lui, Man Yee B.A.; Reuter, Victor E. M.D.; Ladanyi, Marc M.D. Aberrant Nuclear Immunoreactivity for TFE3 in Neoplasms With TFE3 Gene Fusions: A Sensitive and Specific Immunohistochemical Assay, American Journal of Surgical Pathology:June 2003 - Volume 27 - Issue 6 - pp 750-761

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