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CASE REPORT

Diffuse Large B Cell Lymphoma in Wiskott-Aldrich Syndrome: A Case Report and Review of Literature

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Abstract Wiskott-Aldrich syndrome (WAS) is an X linked rare primary immunodeficiency syndrome with an increased propensity for infection, autoimmunity and malignancy. Here we report a male child, who was diagnosed with WAS at 1 year of age following evaluation for symptomatic thrombocytopenia and eczematous skin lesions. He presented later with lymphadenopathy, which was consistent with diffuse large B cell lymphoma on histopathology. He received 6 cycles of R-CHOP chemotherapy for the same and is presently in remission after 6 months. We review the major publications of lymphoma in WAS and discuss the pathological findings, treatment and prognosis of lymphoma in WAS.

Keywords Diffuse large B cell lymphoma · Wiskott-Aldrich syndrome · Primary immunodeficiency syndrome

Introduction

Wiskott-Aldrich syndrome (WAS) is one of the rarer primary immunodeficiency syndromes, presenting in 1–10 per 1,00,00,00 population [1]. Patients usually present with bleeding manifestations secondary to microthrombocytopenia, eczema and recurrent infections [2, 3].Malignancies are commoner in patients with WAS, and these patients usually have a poorer prognosis with a median overall survival (OS) of around 1 year [4]. A male child who was diagnosed with WAS on the basis of family history, clinical presentation, blood parameters and genotypic analysis later went on to develop diffuse large B cell lymphoma (DLBCL) 10 years after initial diagnosis of WAS. This to our knowledge, is the first report from India of a patient with WAS who developed a DLBCL.

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Case Report

A one year old male child, born to non-consanguineous parents, with no significant antenatal, natal or neonatal history, presented with history of purpuric lesions all over the body with occasional bleeding from gums and recurrent respiratory tract infections from six months of age. Clinical examination was insignificant except for eczematous lesions over the scalp and post auricular region and multiple ecchymotic patches over the upper and lower limbs. A similar history was elicited from his parents about his sibling, who had similar complaints and was diagnosed as immune thrombocytopenia elsewhere, had undergone splenectomy for the same and succumbed to post splenectomy sepsis at 6 years of age. With a clinical suspicion of Wiskott-Aldrich syndrome (WAS), he was investigated further. At presentation he had a hemoglobin of 10.6 gm/dl with a total leukocyte count of 9,600/mm^3 (neutrophils-35 %, lymphocytes-45 %).His platelet counts were 15,000/mm^3 with a mean platelet volume of 6 fl. Serum quantitative Immunoglobulin analysis showed normal levels of IgG and IgM with mildly decreased levels IgA of 112 mg % (Ref normal range: 140–420). Mutation analysis revealed a nonsense mutation in exon 10 of the WAS gene at c.961C>T (p.Arg321*) that predicts premature termination of

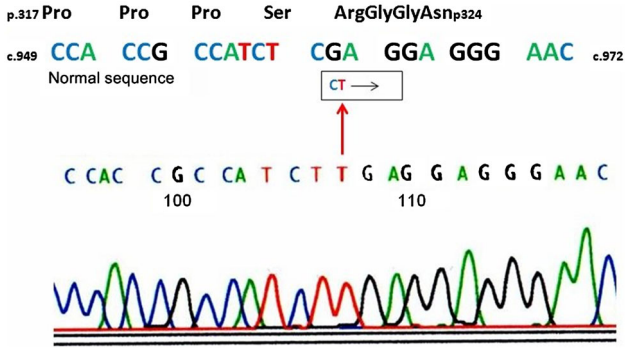

Fig. 1 Electropherogram of WASP gene in the patient demonstrating a c.961C>T mutation. This nucleotide change predicts a p.Arg321* nonsense mutation in the patient

translation of WAS protein confirming the diagnosis (Fig. 1). Genomic DNA from the patient's EDTA anticoagulated blood was isolated by standard phenol-chloroform method. The human *WAS* gene exonic and flanking intronic regions were amplified by six pairs of primers as described previously [5]. Nucleotide changes in the amplified fragments were screened by a conformation sensitive gel electrophoresis (CSGE) and DNA sequencing strategy [6]. Samples displaying abnormal CSGE patterns were sequenced by the Big Dye Terminator cycle sequencing kit (Applied Biosystems, Warrington, UK) on an ABI 3130 genetic analyzer (*PE* Applied Biosystems, Foster City, CA, USA). The patient was offered stem cell transplantation but they deferred the treatment because of the absence of a matched family donor. The patient subsequently was lost to follow up.

He presented 9 years later with left sided neck swelling of 8 months duration. Clinical examination revealed left lower cervical and submandibular lymph nodes (1 × 1 cm), right axillary lymph nodes (3 × 3 cm) and bilateral superficial inguinal lymph nodes (2 × 2 cm). Rest of the clinical examination was unremarkable. His blood investigations showed a hemoglobin of 11.7 gm/dl, a total leukocyte count of 9,900/mm^3 (neutrophils-19 %, lymphocytes-25 %, eosinophils-55 %) and a platelet count of 10,000/mm^3. Abdominal imaging revealed multiple, large, coalescent nodes in the periportal, peri pancreatic and upper para aortic region, upto 3 cm in size. The patient subsequently underwent a right axillary lymph node biopsy which was reported as Diffuse large B cell lymphoma (Large cells: CD 20 positive, CD 30 and CD 15 negative, EBV LMP negative, MIB 1 index-70 %). Atrophic germinal centres typical of Wiskott-Aldrich syndrome were found (Fig. 2). Bone marrow showed reactive eosinophilia with no evidence of lymphoma. He was staged as Ann Arbor IIIA and was started on R-CHOP 21 chemotherapy. He received a total of 6 cycles of chemotherapy with a good response to treatment and a PET CT scan done 3 months after completion of chemotherapy shows him to be in complete remission. He is presently in remission at 6 months of follow up.

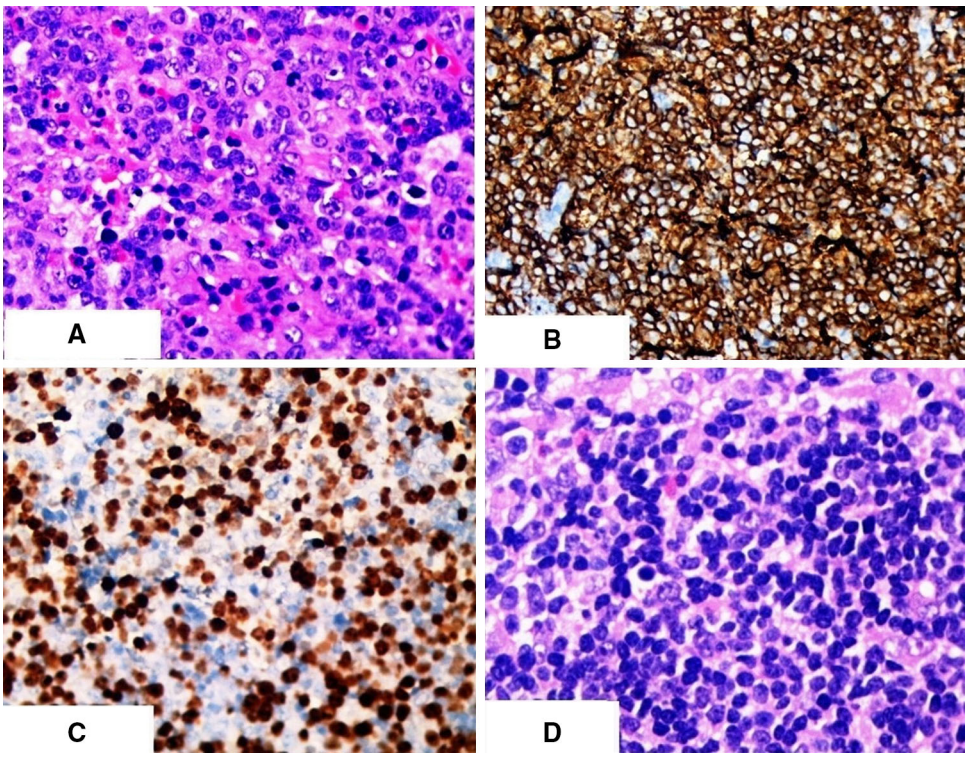

Fig. 2 Axillary lymph node biopsy specimen showing: **a** (×400) Large cells on H & E stain; **b** (×200) CD 20 positive large cells; **c** (×200) MIB 1 staining; **d** (×400) H & E staining characteristic atrophic lymph node follicles in WAS

Table 1 Review of major publications of lymphoma in WAS patients

Author	Type of study	Described lymphoreticular malignancies	EBV status	Presentation	Treatment	Outcome
Cotelingam et al. [4]	Retrospective analysis	$N = 24$ NHL = 8 (7-Diffuse large cell immunoblastic) HL = 1 (Nodular sclerosis)	N/A	Median age-7.8 years NHL-Diffuse disease HL-Cervical and inguinal lymphadenopathy	Chemotherapy based	Median survival <1 year
Perry III et al. [23]	Retrospective analysis	$N = 301$ Lymphoreticular malignancies = 23	N/A	Data not available	Data not available	Data not available
Frizzera et al. [14]	Retrospective analysis	$N = 31$ (Lymphoreticular disorders) WAS = 10 NHL = 5 HL = 1 Unclassified = 1	N/A	Data not available	Data not available	Data not available
Gilson et al. [21]	Case report	DLBCL Ann Arbor IAE	–	16, Male Orbital mass	Chemotherapy Presentation-UKCCSG for localised NHL Relapse-VCE × 6 cycles	Alive till 9 years of last follow up
Palenzuala et al. [24]	Case report	DLBCL Ann Arbor IAE	–	15, Male Acute laryngitis: Laryngeal growth	CVP followed by local RT followed by Laser debulking	Died: Acute respiratory failure following Laser debulking
Nakanishi et al. [25]	Case report	DLBCL Ann Arbor IVB	+	14, Male Aggressive lymphadenopathy, 20 years-Multiple CNS lesions	Local RT	Succumbed to Pseudomonas sepsis
Coccia et al [20]	Case report	DLBCL Ann Arbor IAE	–	15 years, Male Pharyngeal growth	Chemotherapy-LNH 97 with Rituximab at 75 % dose	Alive and in remission at 3 years of last follow up
Kawakami et al. [26]	Case report	Follicular lymphoma with large cell transformation (Heterogeneous histology)	–	21, Male Generalized lymphadenopathy	Not available	Died at 1 year of diagnosis
Kroft et al [17]	Case report	Follicular large cell lymphoma with immnoblastic features t(14,18), c-myc + Ann Arbor IB	–	15, Male B symptoms, submandibular lymphadenopathy	Chemotherapy-CCG, Protocol 5911(regimen 1-Orange arm) MUD transplant in CR	Alive and in remission at 90 days post transplant
Faraci et al. [18]	Case report	Unclassified lymphoma	–	8, Male Abdominal pain, distension. RLQ peritoneal mass involving distal jejunum	Surgical resection with distal jejunectomy -Intestinal obstruction after 6 weeks-Ileal resection (No residual disease)	Died after 4 ½ months-Massive subarachnoid haemorrhage. No residual lymphoma at autopsy
Pasic et al. [16]	Case report	Burkitt's lymphoma	–	12, Male Ileo-colic Intussusception	Terminal ileal resection-Diagnosis on surgical specimen biopsy: Rituximab based chemotherapy	In remission with chemotherapy
Periman et al. [27]	Case report	Hodgkin's lymphoma: Nodular sclerosis	–	16, Male Generalised lymphadenopathy with B symptoms	MOPP chemotherapy-Complete remission: Relapsed after 1 year-RT	Died 19 months after diagnosis of lymphoma
Yoshida et al. [15]	Case report	Hodgkin's lymphoma: Lymphocyte depleted	+	8, Male Bilateral pulmonary hilar lymphadenopathy	ABVD 4 courses followed by local fractionated RT (20 Gy)	In remission at 50 months of follow up
Sebire et al. [28]	Case report	Cutaneous lymphomatoid granulomatosis	+	Isolated, non healing, ulcerated skin lesion	Rituximab for 4 cycles	In remission at 18 months of follow up

NHL Non Hodgkin lymphoma, *HL* Hodgkin lymphoma, *N/A* Not available, *WAS* Wiskott-Aldrich syndrome, *DLBCL* Diffuse large B cell lymphoma, *UKCCSG* United Kingdom Children's Cancer Study Group, *VCE* Vincristine, Cisplatin, Etoposide, *CVP* Cyclophosphamide, Vincristine, Prednisolone, *RT* Radiation therapy, *CNS* Central nervous system, *MUD* Matched unrelated donor, *CR* Complete remission, *RLQ* Right lower quadrant, *MOPP* Mustine (Nitrogen mustard), Oncovin (Vincristine), Procarbazine, Prednisolone, *ABVD* Adriamycin, Bleomycin, Vinblastine, Dacarbazine

Discussion

WAS is a rare X linked primary immunodeficiency syndrome characterized by micro thrombocytopenia, eczematous skin lesions, and recurrent infections [2, 3, 7, 8]. The protein involved, WASP, is encoded by the WAS gene [9]. It is an important regulator of actin polymerization in response to signals from the cell membrane, and is predominantly expressed in hematopoietic cells [1, 3, 8]. WAS gene mutations resulting in mutated WASP can cause full blown WAS to X linked thrombocytopenia (XLT) [10] which is associated with thrombocytopenia without significant immune impairment, and considered an attenuated version of WAS [1, 3, 8]. A recently described gain of function missense mutation at the Cdc42-binding site is associated with X linked severe congenital neutropenia [1, 8, 11].

WASP mutations in WAS and XLT result in micro thrombocytopenia, with a 100 % incidence. Though the mechanism has not been completely delineated, peripheral destruction of platelets is supposed to play a major role [1, 3]. Bleeding is thus the most common manifestation. Eczematous skin lesions are present in around 60–80 % patients [2, 3, 12]. Autoimmune hemolytic anemia is the most common autoimmune manifestation followed by arthritis, cutaneous vasculitis, Henoch Schonlein purpura [1–3] .

Patients with WAS have a high incidence (13–22 %) of tumors [2, 12, 13]. WAS gene mutation affects cells of both innate and acquired immunity, involving NK, B and T cells [1, 3, 7, 8]. Almost 90 % malignancies are of lymphoreticular origin, and have a poorer prognosis than in those with normal WASP protein [2, 3, 8]. As in other primary and acquired immunodeficiency syndromes EBV associated tumors are commoner in WAS patients [14, 15]. Abnormal immune surveillance in WAS patients underlies the increased chance of neoplastic transformation [1, 3, 7, 8]. There is decreased synapse between NK cells and tumor cells in WAS subjects [1] due to decreased actin accumulation at the synapse. This impairs NK cell mediated lysis of tumour cells.

Lymphoma has been widely described in patients with WAS [4, 15–19]. This to our knowledge is the first reported case of a diffuse large B cell lymphoma in a patient with WAS from the Indian subcontinent. Non Hodgkin's lymphoma is the commonest tumor in WAS [4, 19]. The median age of diagnosis is 9.5 years [2]. Response to therapy directed towards the lymphoma is poor in these patients and median survival is around 1 year. Long term survival in WAS patients with lymphoma who has received appropriate chemotherapy have also been reported [20, 21]. Use of anti CD 20 monoclonal might improve the prognosis but awaits larger studies to validate it. Our patient received 6 cycles of R-CHOP chemotherapy after disease staging, and remains in remission at 6 months of follow up. Table 1 shows the major publications of lymphoma in patients with WAS. Allogeneic stem cell transplantation (SCT) from a suitable donor is the only curative therapy available for WAS. SCT has been successfully carried out in a patient with WAS and Non Hodgkin's lymphoma with complete remission of both for over 2 years [22].

Conclusion

WAS is a rare primary immunodeficiency which can present in a myriad of clinical forms. Poor immunological response leads to an increased chance of malignancy, with NHL being the commonest. Prognosis of NHL in WAS remains poor, but the use of anti CD 20 monoclonal can improve the outcome in B cell neoplasms. Transplant remains the only curative therapy presently for WAS.

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