"FDC-only lymphoid follicles" in lymphoid tissue in a young boy with Wiskott-Aldrich Syndrome: a morphologic correlate of defective immune synapse

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Abstract

Wiskott-Aldrich Syndrome (WAS) is an inherited disorder characterized by classical triad of eczema, micro-thrombocytopenia, and immune-deficiency. This disease affects all the three hematopoietic lineages to a variable extent. The spectrum of clinical and laboratory data for WAS has been well described in the literature though there is paucity of its histopathologic correlates. The current case describes the autopsy findings of a case of WAS with specific recognition of altered histology noticed in the lympho-reticular tissues- 'the follicular dendritic cell (FDC)-only lymphoid follicles.' The possible mechanisms of this altered histology has been discussed.

Title page

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Abbreviation key:

IHC Immunohistochemistry

FDC Follicular dendritic cell

WAS Wiskott-Aldrich Syndrome

WASp Wiskott-Aldrich Syndrome protein

Abstract

Wiskott-Aldrich Syndrome (WAS) is an inherited disorder characterized by classical triad of eczema, micro-thrombocytopenia, and immune-deficiency. This disease affects all the three hematopoietic lineages to a variable extent. The spectrum of clinical and laboratory data for WAS has been well described in the literature though there is paucity of its histopathologic correlates. The current case describes the autopsy findings of a case of WAS with specific recognition of altered histology noticed in the lympho-reticular tissues- 'the follicular dendritic cell (FDC)-only lymphoid follicles.' The possible mechanisms of this altered histology has been discussed.

Introduction

Wiskott-Aldrich Syndrome (WAS) is an X-linked recessive disorder characterized by the presence of eczema, micro-thrombocytopenia, and immune-deficiency.[1]The histopathologic correlates of this disease have rarely been described.[2,3] We report the autopsy findings in a case of WAS with special recognition of altered histology in lymphoid tissue: 'the follicular dendritic cell (FDC)-only lymphoid follicles.'[4] The plausible explanation of this morphology correlating with defective immune synapse formation has been discussed.

Case description

A 5-year-old boy presented with a history of recurrent episodes of cough and respiratory distress since day 20 of life. Since the age of two years, he had had recurrent episodes of otitis media. At the age of three, he developed epistaxis (requiring blood transfusion) and eczema all over the body. His younger brother died at 15 months of life. However, details of his illness were not available.

On examination, he had generalized lymphadenopathy, eczema, and cutaneous bleeds. The rest of the examination was unremarkable. A clinical possibility of WAS was considered. Laboratory investigations revealed anaemia (haemoglobin of 113 gm/L), eosinophilia (1.3510^9 cells/L), and thrombocytopenia (8×10^9/L). The mean platelet volume was 9.5 fl (N=7-11 fl) **(Figure 1A)** . He had elevated IgA (423 mg/dl; N-50 -240 mg/dl) and IgE (2058 IU/L) with normal IgG (1331 mg/dl; N-540 -1610 mg/dl) and IgM (57 mg/dl; N-50-180mg/dl). WAS protein (WASp) expression was reduced **(Figure 1B),** and genetic analysis for the *WAS* gene revealed a hemizygous single nucleotide deletion resulting in an alteration in the reading frame and premature termination (c.941delC, p.P314Rfs94X) **(Figure 1C).** His clinical WAS score was 4. He was initiated on monthly replacement intravenous immunoglobulin (IVIg) therapy (400 mg/kg) and cotrimoxazole prophylaxis (5 mg/kg trimethoprim component). He remained clinically well for next the three years. At eight years, he was hospitalized with complaints of epistaxis and headache. At 20 hours of hospital stay, he started developing vomiting with features of raised intracranial pressure. Non-contrast computerized tomography revealed intracranial bleed. He also developed subconjunctival haemorrhage, and a fundus examination showed

retinal haemorrhages. On day 2 of hospital stay, he developed pulmonary haemorrhage requiring ventilation. He was given multiple platelet transfusions, IVIg, and intravenous methylprednisolone. On day 3 of illness, he developed shock and cardiac arrhythmia and succumbed to illness. An abdomino-thoracic with brain autopsy was carried out.

At autopsy, he had multiple ecchymotic patches all over the body. There were enlarged hilar, peripancreatic, mesenteric, preaortic, and para-aortic lymph nodes measuring 1.5-3 cm **(Figure 2, A & B)** . Abdominal lymph nodes were present as conglomerate masses with a homogenous cut surface. All these lymph nodes had similar histology**(Figure 2, C & D)** . The architecture was partly effaced with the expansion of interfollicular and paracortical areas. The most striking finding was the presence of markedly atretic hyalinized germinal centres that have been reported previously as 'FDC-only lymphoid follicles.'[4] These were surrounded by the variable thickness of the mantle zone. The cells comprising the follicle centres were plump-shaped epithelioid cells with abundant pink cytoplasm, scattered macrophages, and a very few lymphoid cells (centroblasts/centrocytes). On immunohistochemistry (IHC), CD20 highlighted a lesser proportion of B-cells in the germinal centres and mantle zone **(Figure 2E)** . Also, there was an extensive paucity of CD10+ follicular centre cells **(Figure 2F)** . A few CD30+ immunoblasts and CD138+ plasma cells were present in the interfollicular areas. CD3 highlighted a variable amount of positivity in T-zone**(Figure 2G)** . CD23 revealed follicular dendritic meshwork of variable sizes ranging from normal to extensively atretic**(Figure 2H)** . Extensive proliferation of high endothelial venules (CD31+) and interdigitating dendritic cells (S-100+/CD1a-) were present in paracortex **(Figure 2I)** . No definite lymphomatous process could be identified. Most lymphoid follicles of the mucosa-associated lymphoid tissue also showed similar histomorphology. The spleen was grossly unremarkable **(Figure 2J)** with appropriate weight for age (75 gms; N- 80+/-5 gms). On microscopy**(Figure 2, K-N)** , a similar picture of white pulp lymphoid follicles was appreciated. Most of these had follicular dendritic cells in the centre surrounded by variably attenuated marginal zone. The T-zone in the periarteriolar region was discontinuous, as highlighted by CD3 IHC. Red pulp had congested sinusoids. Bone marrow revealed normal trilineage haematopoiesis. The thymus gland showed normal histology of preserved B/T cells and intraparenchymal haemorrhages **(Figure 2, O-Q)** .

The leading cause of death was tonsillar herniation due to extensive cerebellar vermis bleed with extension into the third and fourth ventricle, and subarachnoid space **(Figure 2, R & S)** . Fresh haemorrhages were also noted in the oesophageal and gastric submucosa, pulmonary parenchyma, biliary tract, and pericardium.

Duscussion

Defect in WASp involved in actin polymerization, is the primary pathogenic event in WAS.[5] This protein is exclusively expressed in the cytoplasm of hematopoietic cells. All the hematopoietic lineages are variably affected depending on the residual activity of WASp. Defective myeloid lineage leads to ineffective phagocytosis and chemotaxis.[6,7] Thrombocytopenia has been attributed to the intrinsic platelet abnormalities or immune-mediated clearance.[8] Bleeding is a common manifestation of WAS. However, life-threatening intracranial bleeding, as was seen in the present case, has rarely been reported.[9]

Abnormal immune synapse formation is seen because of defective interactions between B, T, and NK cells.[10] However, there is a paucity of data with regard to the morphological counterpart of these pathophysiological mechanisms that can be visualized on a pathology specimen.[5] We identified these alterations in the lymph nodes, spleen, and thymus in a patient with WAS using conventional histology and IHC. In addition, we also looked at the spectrum of pathological changes in other organs.

The distinct pathology of 'FDC-only lymphoid follicles' in lymph nodes of organ transplant recipients was first described by Mitsunori et al.[4] Authors attributed this morphology to the effects of immunosuppressive therapy, causing augmentation of apoptosis of germinal centre lymphoid cells as well as reduced migration of lymphocytes to lymph nodes. The present case demonstrates a marked paucity of germinal centre cells and variable reduction of cells in the mantle zone, marginal zone, and T-zone. This may be attributed to defective WASp, which regulates cytoskeleton, ultimately causing membrane alterations and increased apoptosis. Although steroid therapy was given to this patient pre-terminally, this is unlikely to be responsible

for the formation of FDC-only lymphoid follicles in a widespread manner.[11]

Vermi et al.[3] described the splenic histology in WAS patients where they also observed depletion of the white pulp as well as reduction of the marginal zone. Similar hyalinized follicles were noticed in their cases as well. The authors postulated that paucity of marginal zone cells might be responsible for an ineffective immune response to T-cell independent antigens. A correlation with the degree of immune cell depletion and WAS score was also shown.

Similar histopathology of lymph nodes has also been reported in patients with Castleman disease (hyaline vascular type). However, the histopathology in Castleman disease has a prominent mantle zone in a typical onion skin fashion compared to an attenuated mantle zone, as was seen in the index case. Pattern 'B' of HIV lymphadenitis is also characterized by atrophic 'burned-out' follicles, and the presence of this morphology recapitulates an immunodeficient state, as was seen in the present case.[12]

To conclude, this case highlights the morphologic correlates of the crippled immune system in a patient with WAS.

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Figure legends:

Figure 1 (**A**). Peripheral blood smear highlighting the normal morphology. The mean platelet volume was 9.5 fl. (**B**). Flow cytometry histogram depicting reduced expression of WASp in case (orange) compared to control (green). (**C**). Sanger sequencing of the *WAS* gene revealed a deletion mutation (c.941delC, p.P314Rfs94X).

Figure 2. Mesenteric (**A**) and Para-aortic (**B**) group of enlarged lymph nodes were dissected at the time of autopsy, having a homogenous cut surface (yellow oval). (**C**). Microscopy of these lymph nodes showing spaced out follicles due to paracortical expansion (black arrow with two heads). (**D**). The follicles are composed of predominantly pink-colored epithelioid cells (*), few scattered macrophages, and a thin mantle zone. IHC for CD20 (**E**), CD10 (**F**), and CD3 (**G**) highlights the reduced number of B-cells in the follicle centre and mantle zone, the follicular centre cells, and the T-cells, respectively. (**H**). The follicle centre cells are represented mainly by CD23 positive follicular dendritic cells. (**I**). Paracortical areas show prominent S-100 positive interdigitating dendritic cells. (**J**). Gross photograph of spleen showing normal architecture. (**K**). Microscopy of spleen showing depleted white pulp with a prominent pink-colored centre representing hyalinized follicles (**L**) with FDCs and attenuated marginal zone (arrow with two heads). (**M-N**). CD3 and CD20 IHC, respectively, highlighting the depleted white pulp in T-cells and B-cells zone. (**O**). Microscopy of the thymus gland showing fresh intraparenchymal hemorrhages. (**P-Q**). CD 3 and CD20 immunostains highlighting the normal distribution of T-cells and B-cells, respectively. (**R**). Gross photograph of the cerebellum with extensive hemorrhages in the vermis. (**S**). Microscopy of cerebellum showing hemorrhagic infarct in the cortex (arrow) and blood accumulation in between cerebellar folia (circle).