Adult Onset Still's Disease With Multiple Lymphadenopathy: a Case Report and Literature Review

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Case Report

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Abstract

Background: Adult onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder that often presents with systemic multiple lymphadenopathy. In addition to the common paracortical and mixed patterns in AOSD lymph nodes histopathological features, the other morphological patterns include diffuse, necrotic, and follicular patterns. However, there have been very few reports to date on the histopathological description of AOSD lymph nodes.

Case presentation: An 18-year-old female presented two months earlier with pain in her large joints with painless rash formation, bilateral posterior cervical lymph nodes, left supraclavicular lymph nodes and left posterior axillary lymph nodes enlargement, and no tenderness. Left cervical lymph node resection was performed for pathological examination. Histologically, lymph node structure is basically preserved, subcapsular sinus, medullary sinus structure exists, there is a lot of histiocytes in the sinus, cortical area is reduced, a few lymphoid follicles of different sizes can be seen, some atrophy, some hyperplasia. The lymphoid tissue in the paracortical region of the lymph node was diffusely proliferative and enlarged, mainly composed of histiocytes with abundant cytoplasm, immunoblasts, and numerous lymphocytes with slightly irregular small to medium-sized nuclei. Nuclear karyorrhexis was easily observed, showing a few nuclear debris and the “starry sky” phenomenon, accompanied by abundant branching high endothelial small vessels with a background of scattered few plasma cells and eosinophil infiltration. Immunohistochemically, lymphoid follicle immunophenotype with reactive proliferative changes. About 40% of the cells in the paracortical region were positive for Ki-67, and the histiocytes expressed CD68, CD163, some expressed S-100, and no MPO. The immunoblasts expressed CD30, CD20, and not ALK or CD15. Background small to medium-sized T cells express CD2, CD3, CD5, CD7, CD4, and CD8, the number of CD8 positive T cells is slightly predominant, and a small number of T cells express GRB and TIA-1. The patient received comprehensive medical treatment after operation, and the condition was stable without progression at the 11-month follow-up evaluation.

Conclusion: The presentation of morphologic cases of AOSD lymphadenopathy will increase the awareness of AOSD among pathologists and clinicians, and aid in the diagnosis and differential diagnosis of AOSD lymphadenopathy from other reactive lymphadenopathies and lymphomas.

Background

Adult onset Still's disease (AOSD) is a rare group of systemic autoinflammatory diseases with complex, incompletely defined etiology and pathogenesis, mainly characterized by intermittent hyperthermia, transient skin rash, elevated blood leukocytes (neutrophils > 80%), polyarthritic pain, multiple lymphadenopathy, and a predilection for young adults [1]. In 1971, Eric Bywaters first described 14 cases of Still's disease occurring from 17 to 35 years of age with clinical features very similar to those of childhood still's disease, mainly characterized by high fever, multiple skin rashes and polyarthritis, thus defining AOSD [2]. Adult still's disease is often accompanied by liver and spleen enlargement and lymphadenopathy, and the clinical manifestations are complex and unspecific, sometimes similar and

overlapping with lymphoma in clinical manifestations and histopathology [3], which may easily lead to misdiagnosis or missed diagnosis.In this review, we describe a case of adult onset Still's disease and review the relevant literature to explore the clinical features, pathomorphologic features of enlarged lymph nodes, and immunophenotype, with the aim of improving the level of pathologic diagnosis of the disease so as not to be misdiagnosed as lymphoma or other associated lymphadenopathy.

Case Presentation

Patient, female, 18 years old. Two months earlier there was no obvious trigger for the development of pain in large joints of all extremities with pruritic and painless rash formation on the skin of the dorsum of the shoulders(Fig.a), both wrists and both sides of the thighs, which worsened with increasing symptoms with febrile and night sweats on admission at 6 days. Admitted to the hospital for blood investigation: ferritin 466.4ng/ml, C-reactive protein 82.7mg/l, IL-6 (85.12pg/ml), white blood cells 15.55×10^9 / L (89.3% neutrophils), antinuclear antibody positive, but RF、ANCA, etc. were negative. Since onset, the patient lost 5kg of body weight. Examination revealed bilateral posterior cervical lymph nodes, left supraclavicular lymph nodes and left posterior axillary lymph nodes without tenderness. Clinical suspicion of lymphoma, left neck lymph node resection was performed for pathological examination.

Pathological findings

One lymph node, approximately 2.5×2×1.2cm, cut surface is grey white, grey red and medium in texture.

The lymph node structure was partially preserved, the subcapsular sinus and medullary sinus were slightly dilated, and the sinus contained a larger amount of histiocytes (Fig.b).The cortical areas were atrophic and smaller, and a few lymphoid follicles of various sizes were seen, some of the follicular germinal centers were atrophic and smaller, some follicles were hyperplastic and enlarged, and there was a “starry sky” phenomenon (Fig.c).The paracortical areas of the lymph nodes were diffusely hyperplastic and enlarged, and were mainly composed of abundant histiocytes, immunoblasts, and numerous hyperplastic medium-sized, slightly irregular nuclei containing T lymphocytes, against a background scattered with a higher amount of plasma cells and a few eosinophils infiltrating (Fig.d).In some areas, histiocyte hyperplasia was patchy, only a few small T lymphocytes were scattered in the primary paracortical area, and a few proliferating histiocytes had distorted and elongated nuclei with irregular morphology (Fig.e).In some areas, the immune blasts proliferate and become “mottled”, apoptotic nuclear debris, histiocyte phagocytosis of nuclear debris. T lymphocytes of medium size were actively proliferative, karyorrhexis was easily seen, and the proliferation of high endothelial venules in the paracortical area showed a complex branching pattern (Fig.f).

Immunohistochemical findings

Proliferating histiocytes expressed CD68, CD163, some expressed S-100 (Fig.g), and some expressed MPO. The proliferating immunoblasts were strongly and weakly heterogeneously positive for CD30 and CD20 and negative for CD15.The proliferating medium-sized T lymphocytes in the paracortical areas

expressed CD3, CD5, CD4, and CD8, with a slight predominance of CD8 positive cells (Fig.h), and some T cells expressed GrB, TIA-1.About 40% of the hot spot areas of Ki-67, a proliferative index in the paracortical region were positive, and plasma cells expressed CD138 but not IgG4.Proliferating or atrophic lymphoid follicles express CD20, CD10, bcl-6, etc.,the Ki-67 proliferation index is about 80%, and do not express bcl-2.CD123, CD56, TDT, ALK and CK antibodies were not expressed.

The patient received comprehensive medical treatment after operation, and the condition was stable without progression at the 11-month follow-up evaluation.

Discussion And Conclusions

Clinically AOSD patients are relatively rare, with an incidence between approximately 1 and 34 per 1 million population, equal incidence in both genders, and a "bimodal" age of onset, 15-25 and 36-46 years, respectively [4]. AOSD often has four major clinical features: transient rash in the proximal limbs or trunk at the peak of fever, high fever of 39°C or more, elevated peripheral white blood cell count and neutrophil proportion greater than 80%, generalized polyarticular pain or arthritis. Other clinical manifestations include: pharyngeal pain, myalgia, myositis, lymphadenopathy, splenomegaly, pericarditis, myocarditis, pleuritis, lung disease, hepatitis, increased erythrocyte sedimentation rate and CRP levels, increased ferritin, decreased glycosylated ferritin and coagulopathy [5]. According to the course of the disease, AOSD patients can be divided into three different clinical patterns: a monocyclic pattern, a multicyclic pattern, and a chronic pattern [4]. AOSD can be easily misdiagnosed clinically as infectious lesions or other diseases, because clinical symptoms and laboratory tests are not specific, such as fever, arthralgia, elevated white blood cells. Clinicians are not aware of the possibility of AOSD when conservative treatment fails. After futile antibiotic treatment like the case presented here, AOSD was finally diagnosed by pathological examination of biopsied lymph nodes. Studies have shown that the general time from the appearance of symptoms or signs to the final diagnosis of AOSD ranges from 1.5 years to 4 years [6].

Adult onset Still's disease (AOSD) usually presents with high fever, arthralgia, rash, and is often accompanied by multiple lymphadenopathy and hepatosplenomegaly [7].When malignant lymphoma is easily suspected clinically after conservative medical treatment is ineffective, pathological biopsy of lymph nodes is the inevitable choice, combined with pathomorphological features, immunohistochemistry and molecular biological examination to confirm the diagnosis.Y K Jeon et al [8] summarized the pathohistomorphological changes in 12 AOSD enlarged lymph nodes and classified the lymphadenopathy into four morphological types. The first atypical paracortical hyperplasia pattern ,characterized by hyperplasia in the paracortical areas of the lymph nodes with abundant high endothelial vessels, was composed mainly of reactive proliferating T lymphocytes, scattered large activated B / T immunoblasts and few plasma cells and eosinophils, with a ratio of CD4 to CD8 positive T lymphocytes of approximately 3:2,And mildly hyperplastic histiocytes and focally hyperplastic monocytoid B cells were seen. And the second burnt out histiocytic pattern, characterized by hyperplasia of the paracortical areas, high endothelial vascularity, and sinus histiocyte proliferation with no remnants of lymphoid follicles. Histiocytes expressed CD68 and S-100 and often clustered in a mottled pattern in the cortical areas. And

the third exuberant immunoblastic reaction pattern, characterized by patchy or diffuse proliferation of numerous immunoblasts in the paracortical area, predominantly t immunoblasts with numerous mitotic figures and a Ki-67 proliferation index of up to 90%, which is most easily confused with malignant lymphoma. The fourth follicular hyperplasia pattern, is characterized by numerous lymphoid follicles of various sizes distributed throughout the lymph nodes, some with enlarged germinal centers, some with atrophy of germinal centers, and vascular hyalinization with widening of mantle or marginal zones. The histomorphological features of AOSD lymphadenopathy are complex and diverse, and change dynamically with the course of the disease.

Hyoun ah Kim et al [9] performed histological observation of lymphadenopathy in 48 AOSD patients and summarized 6 morphological patterns of lymph nodes. These include: follicular pattern, dominated by extensive hyperplasia of lymphoid follicles; Paracortical areas pattern, with proliferation and expansion of the paracortical areas and only a few small remnants of lymphoid follicles; Diffuse pattern, diffuse hyperplasia of the paracortical areas, no lymphoid follicular structures seen; Necrotic pattern, proliferative expansion of the paracortical areas, focal scattered necrosis and nuclear fragmentation; Mixed patterns of lymphoid follicles and paracortical areas; And a mixed pattern of diffuse and paracortical areas. It is also mentioned in the text that in almost all morphologic patterns, moderate to severe hyperplasia of histiocytes is seen, and there are more CD8 positive T cells than CD4 positive T cells. The morphologic features of lymph nodes in our case should belong to the mixed pattern of lymphoid follicles and paracortical areas, which were expanded with proliferative and atrophic lymphoid follicular structures, and a slight predominance of CD8 positive T lymphocytes.

AOSD patients often present with multiple enlarged lymph nodes, and when the diagnosis is still difficult to be established by a combination of clinical manifestations, laboratory tests, and imaging studies, surgical resection with pathological biopsy of lymph nodes is the inevitable choice for the final definite diagnosis. Previous articles have shown that most lymph node lesions histomorphometrically exhibit reactive hyperplasia in the paracortical region, characterized by the proliferation of immunoblasts and high endothelial venules [9-10]. The histomorphological features of AOSD lymphadenopathy are complex and diverse, and change dynamically with the course of the disease, which still needs to be differentiated from the following diseases.(1) Angioimmunoblastic T-cell lymphoma(AITL): AITL is a T-cell lymphoma formed by the proliferation of mature follicular helper T cells with prominent hyperplasia of high endothelial venules and follicular dendritic cells, often showing generalized lymphadenopathy, hepatosplenomegaly, systemic symptoms and polyclonal hypergammaglobulinemia, and often a rash with pruritus. There are many similarities between AITL and AOSD in clinical presentation and histomorphologic features, with the former neoplastic cells often expressing CXCL13, PD1, CD10, BCL6, and ICOS, most cases often showing EBV positive B cells, and an irregular proliferation of CD21 positive follicular dendritic cells surrounding high endothelial venules.□2□Dermatopathic lymphadenopathy(DL)□ DL is a special type of proliferative lesion of the paracortical region of lymph nodes that usually presents as lymphadenopathy in the drainage area with chronic skin irritation. Histomorphology often shows a pale nodular appearance in the paracortical region, which is mainly composed of proliferating interdigitated dendritic cells, Langerhans cells, and pigment laden histiocytes. Some studies have shown

that in dermatopathic lymphadenopathy lesions [11], the paracortical areas of lymph nodes contain at least three subsets of dendritic cells with different immunophenotypes: interdigitated dendritic cells (S100 positive, CD1a sparsely positive, langerin negative), Langerhans cells (S100 positive, CD1a positive, langerin positive) and few dendritic cells (S100 positive, CD1a negative, langerin negative).[3] Infectious mononucleosis(IM):IM is an EBV infection induced proliferative lesion of lymph nodes and tonsils, commonly seen in adolescents and young adults, has a short disease course, and histologic features vary with disease duration. Lymphofollicular hyperplasia predominates early in the disease, with monocytoid B-cell and histiocytic hyperplasia. The later stages of the disease show proliferative expansion in the paracortical areas, composed of proliferating immunoblasts, small to medium-sized lymphocytes, and plasma cells with a mottled appearance, dominated by CD8 positive T cells, and the immunoblasts often show EBER positivity.(4) Histiocytic necrotizing lymphadenitis (Kikuchi's disease): also known as Kikuchi Fujimoto lymphadenitis, usually has a self limited, predilection for young adults, especially young Asian women. It is classified into three different subtypes: proliferative, necrotic, and xanthomatous. The early stage was dominated by the proliferation of immunoblasts, crescentic histiocytes, and plasmacytoid dendritic cells in the paracortical region. The necrotic phase showed patchy necrosis without neutrophil infiltration in the paracortical area, with a large number of nuclear debris. The xanthoma stage contains a large number of foamy histiocytes and few immunoblasts. When AOSD lymphadenopathy appears in a necrotic pattern, it needs to be differentiated from Kikuchi's disease, and the simultaneous appearance of both lesions has also been documented [12].

Depending on the course of the disease, AOSD patients have been clinically classified into three different clinical patterns (monocyclic, multicyclic, and slowly progressive) [13-14]. The chronic progression pattern is most commonly characterized by the occurrence of at least one persistent symptom lasting more than one year, mainly characterized by stable disease progression, persistent inflammation and often erosion of the affected joint. Followed by a multicyclic pattern, manifesting as periodic recurrences with unpredictable deterioration months or years later. A monocyclic pattern, manifesting as a single episode over 2 months but less than 1 year, persisted in remission with no recurrence throughout follow-up. A new approach has divided AOSD patients into two phenotypes: those with systemic features and those with chronic arthritis as the predominant feature [14].

AOSD often presents as a chronic passage, and patients may develop different complications within the course of the disease, which affect their clinical condition, treatment, and prognosis. Secondary hemophagocytic lymphohistiocytosis (HLH), aka macrophage activation syndrome (MAS), is the most severe complication and is associated with high mortality. Common complications are coagulopathy with multiorgan involvement including heart, lung, liver, spleen and other sites [15-16], and these patients often require more intensive treatment and have a worse prognosis. It has been shown that more than 20% AOSD patients experience recurrence and that patients with severe disease at the initial stage of the disease may be at an increased risk of recurrence, which requires intensive treatment and close follow-up [17].

Abbreviations

AOSD: Adult onset Still's disease; CRP: C-reactive protein; AITL: angioimmunoblastic T-cell lymphoma; DL: Dermatopathic lymphadenopathy; IM: Infectious mononucleosis; HLH: hemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome;

Declarations

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Authors' contributions

ZHH conceptualized and wrote the manuscript. HX collected clinical data. QQM performed pathological diagnosis and immunohistochemical analyses. All authors have read and approved the final manuscript prior to submission.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request

Ethics approval and consent to participate

This case study was approved by the Institutional Review Board for ethical committee of Shenzhen Hospital of traditional Chinese medicine.

Consent for publication

Written informed consent for publication of the clinical details and images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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Figures

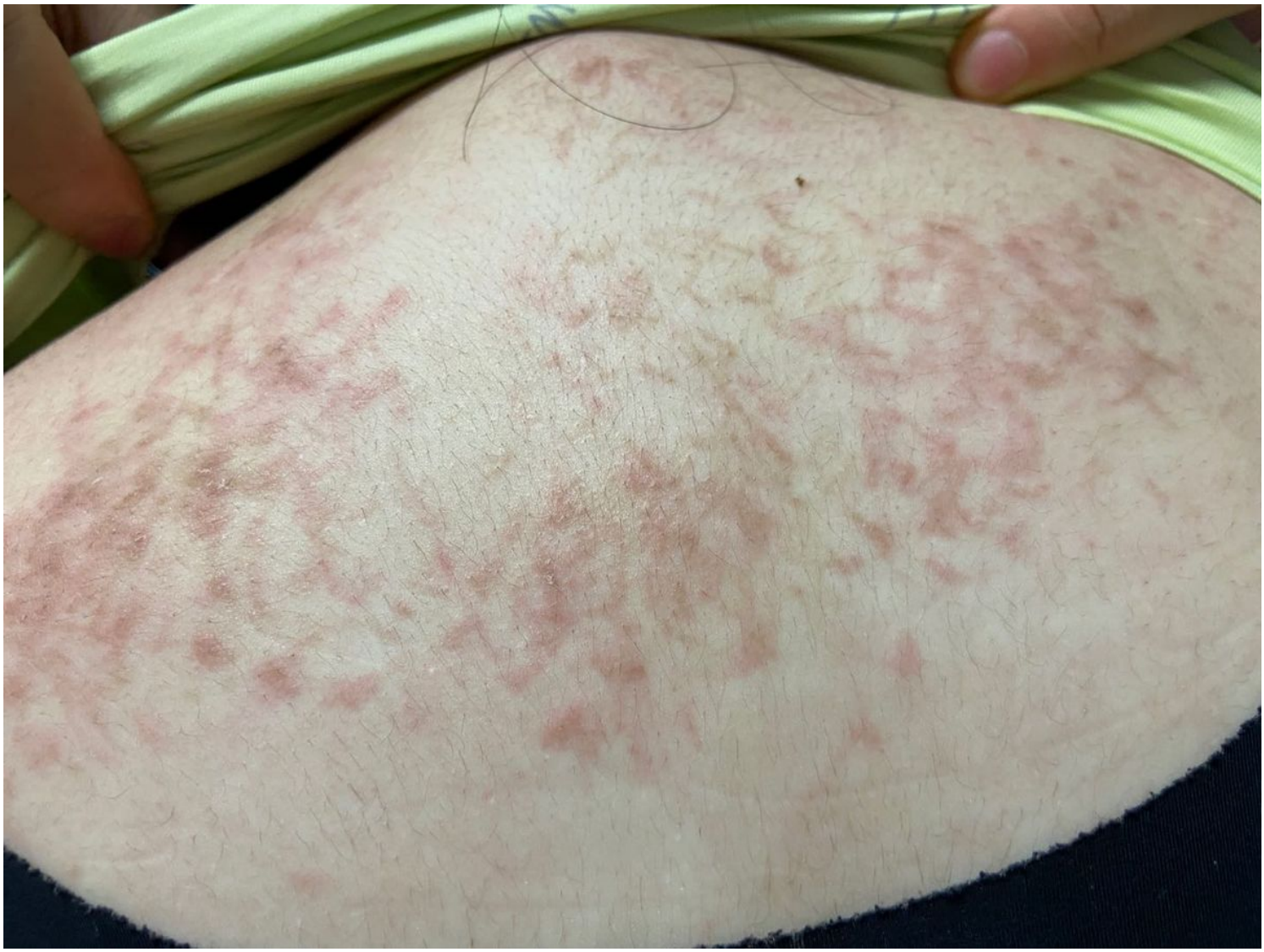

Figure 1

Pruritus and painless rash developed on the back and shoulder skin of the patient.

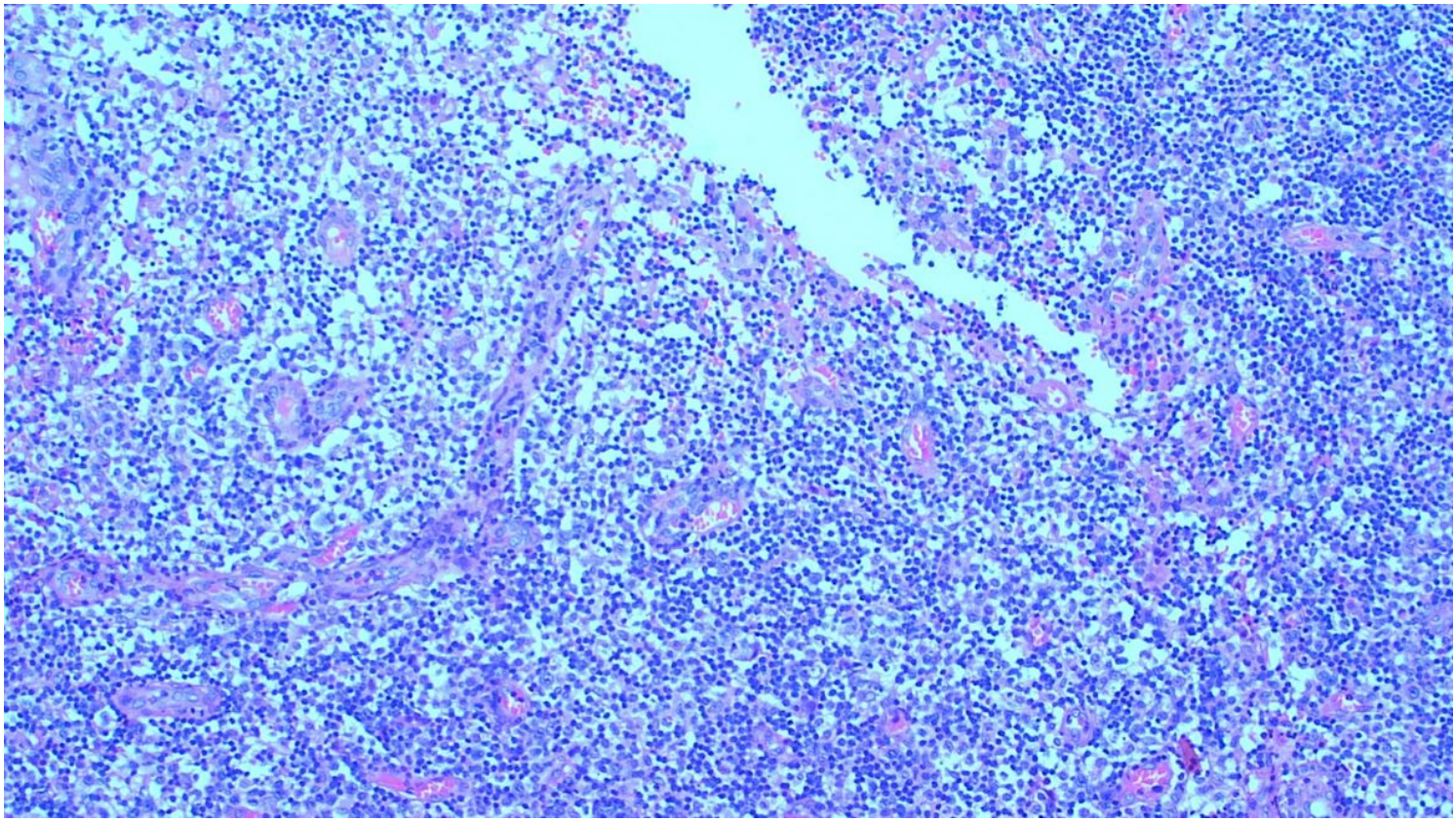

Figure 2

lymph node structure is partially preserved, the subcapsular sinus and medullary sinus are slightly expanded, and the sinus contains a larger amount of histiocytes.

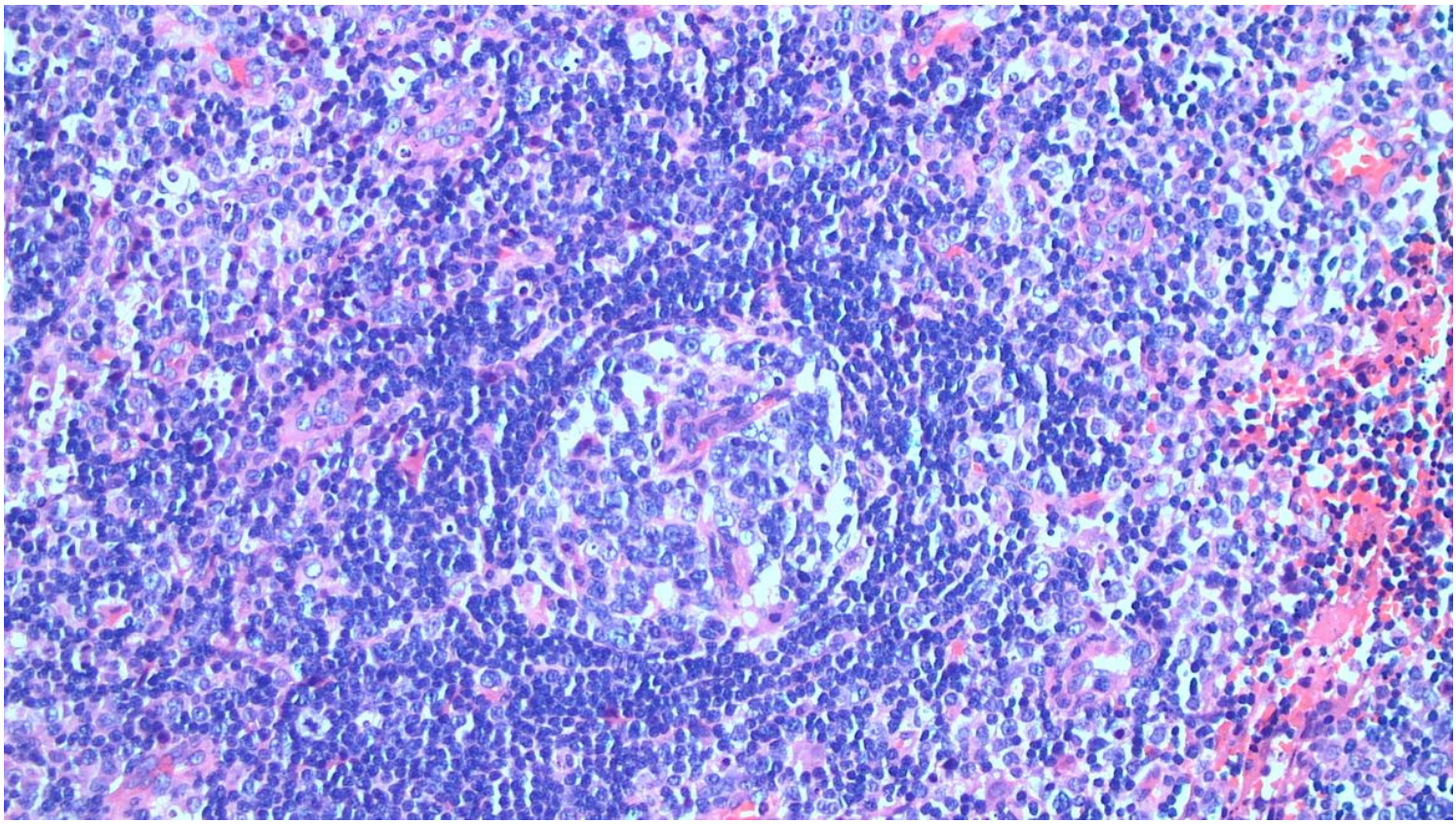

Figure 3

The cortical areas are atrophic and smaller, a few lymphoid follicles of various sizes are seen, and some of the follicular germinal centers are atrophic and smaller.

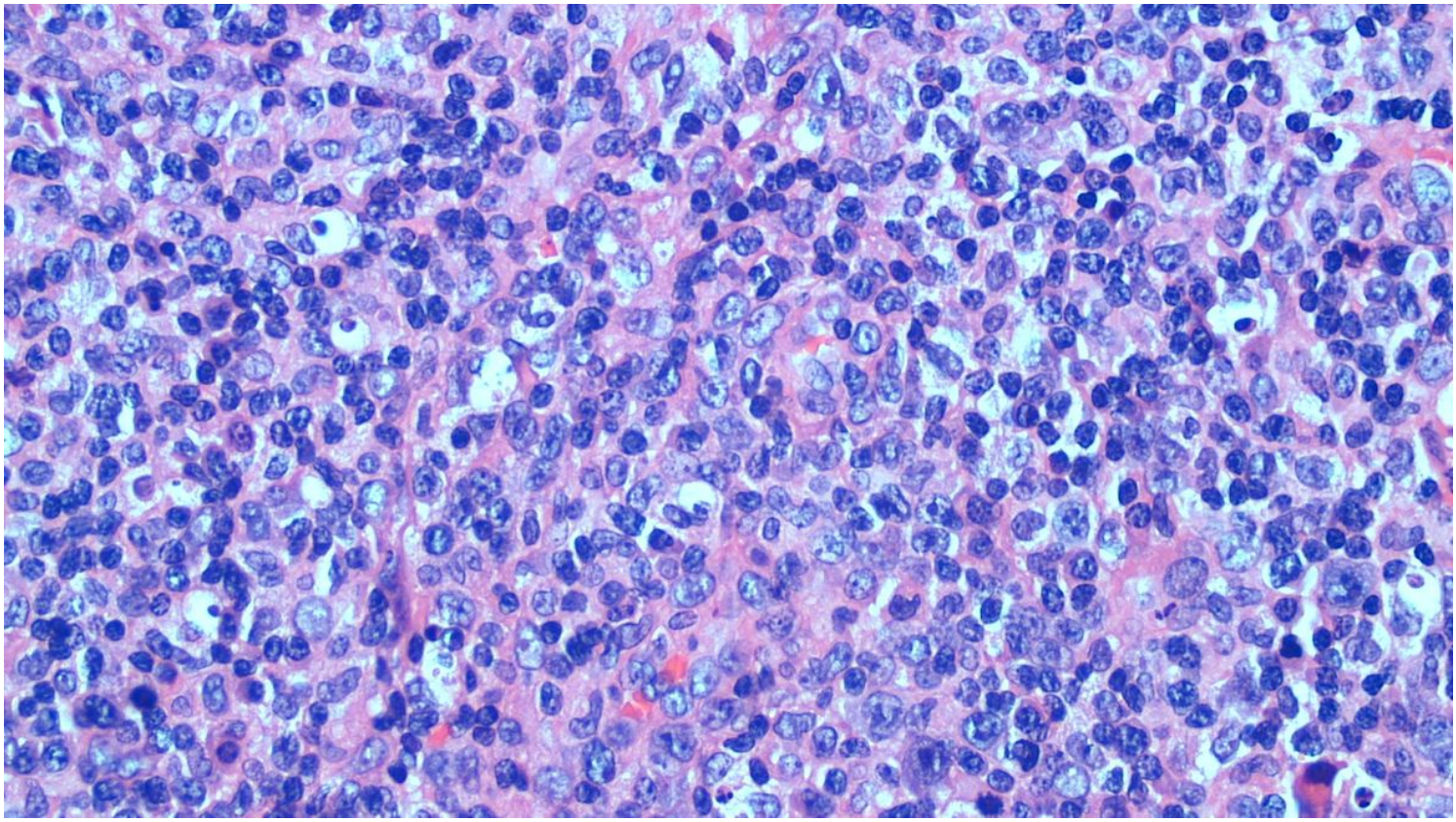

Figure 4

lymph node paracortical areas are diffusely proliferative and enlarged, and consist mainly of histiocytes, immunoblasts, and medium-sized T lymphocytes.

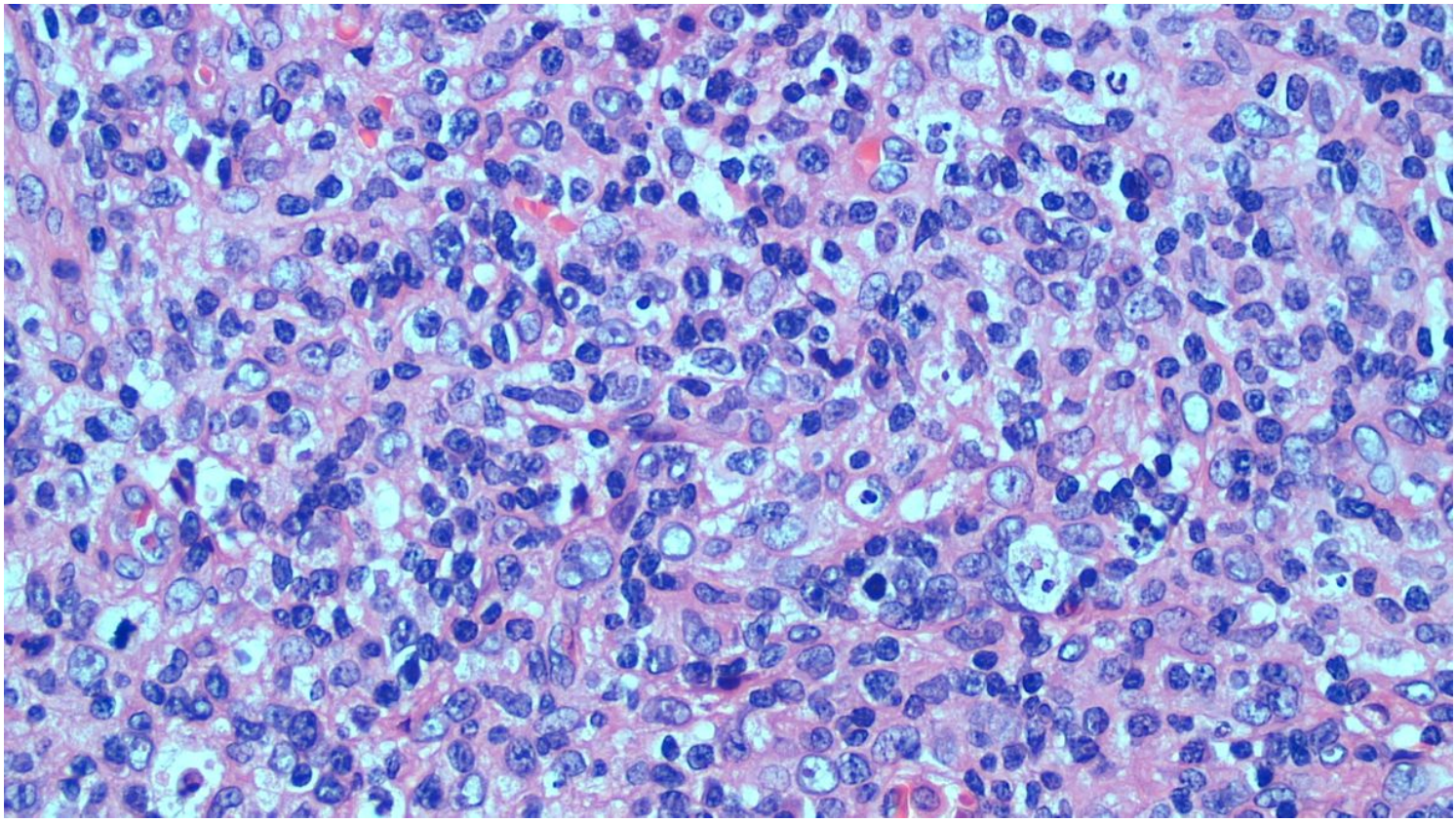

Figure 5

A small number of histocyte had distorted and elongated nuclei with irregular shape.

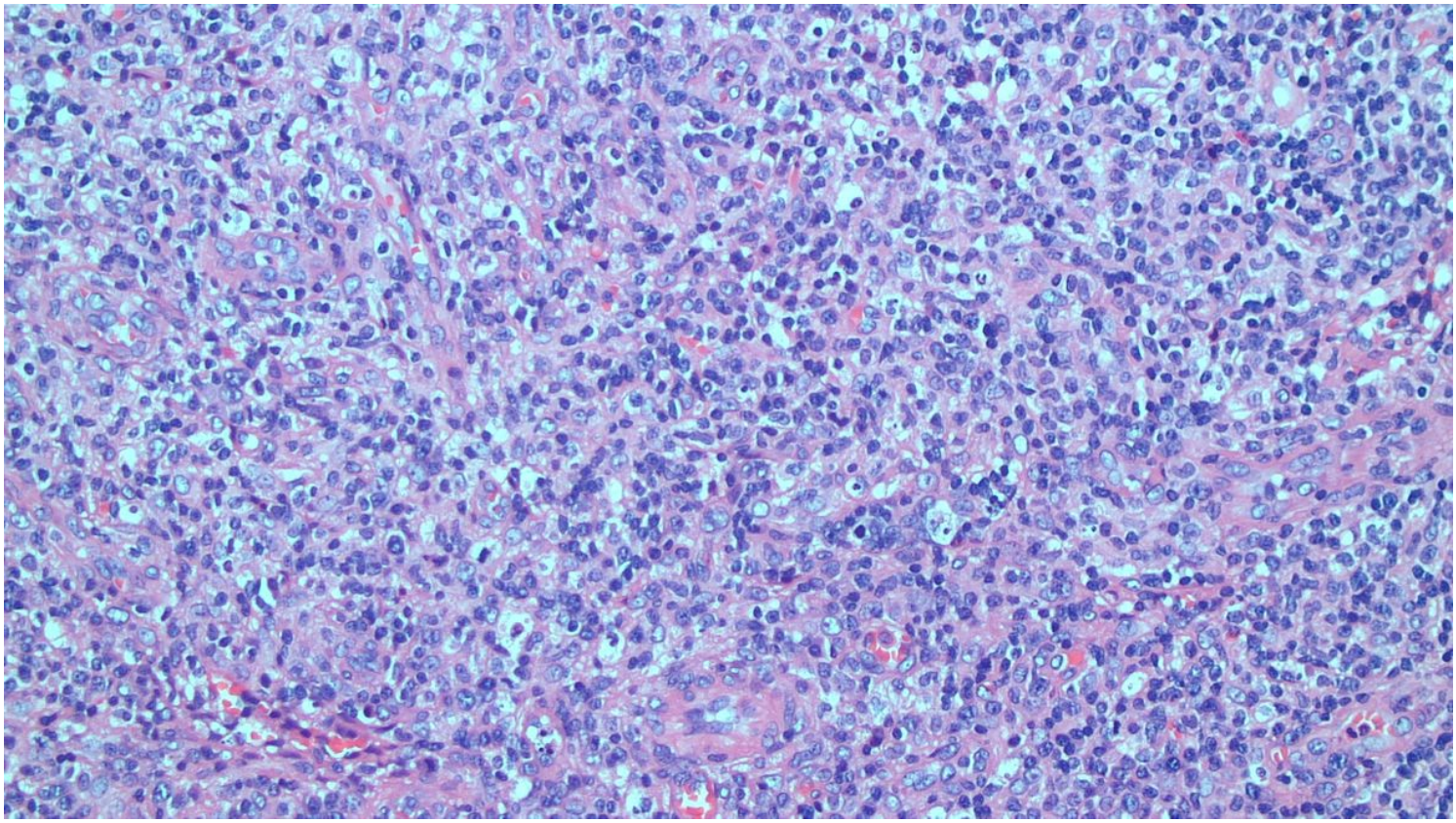

Figure 6

High endothelial venule proliferation in the paracortical area.

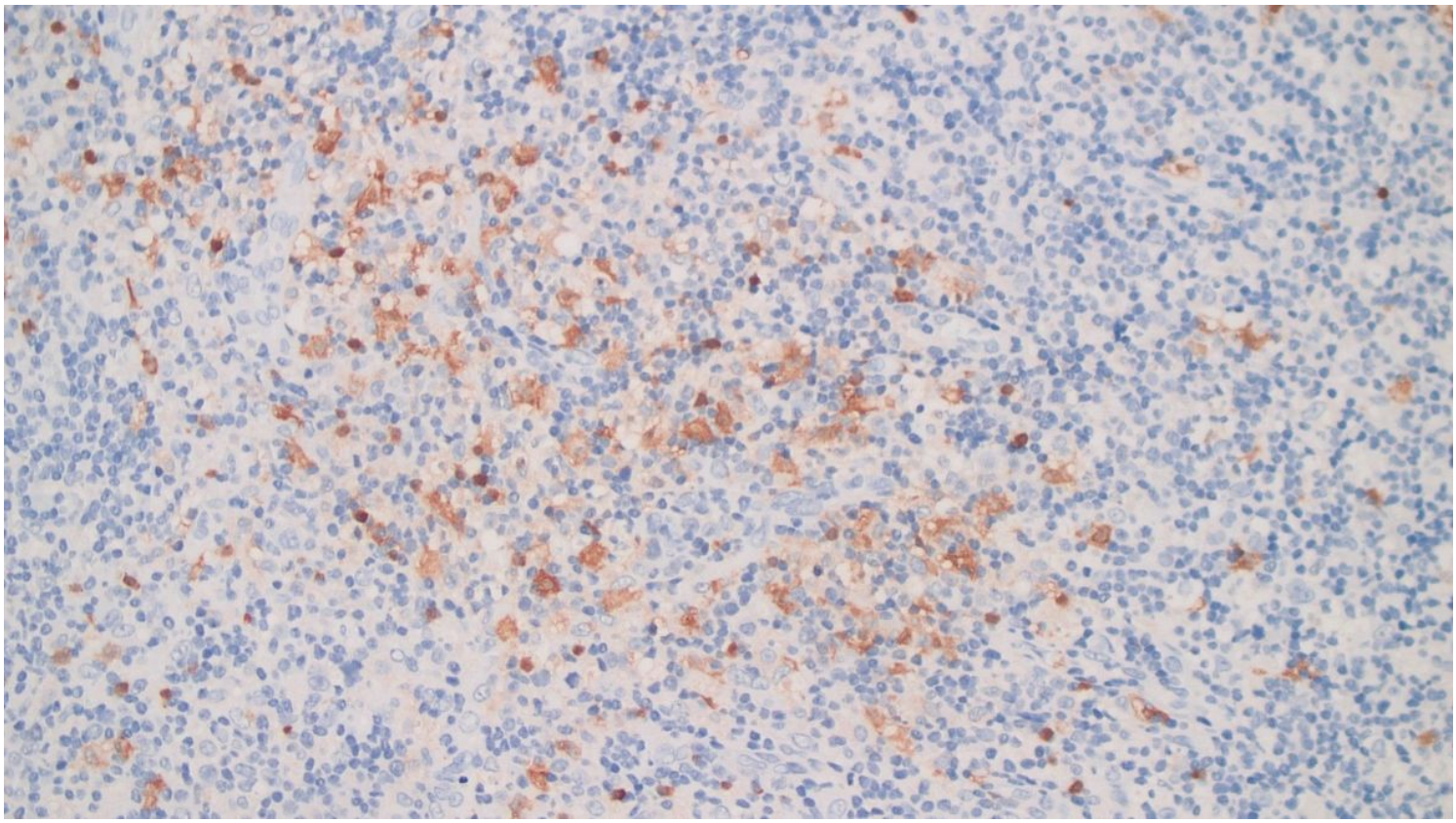

Figure 7

The proliferating histiocytic fraction of the paracortical area expresses S-100.

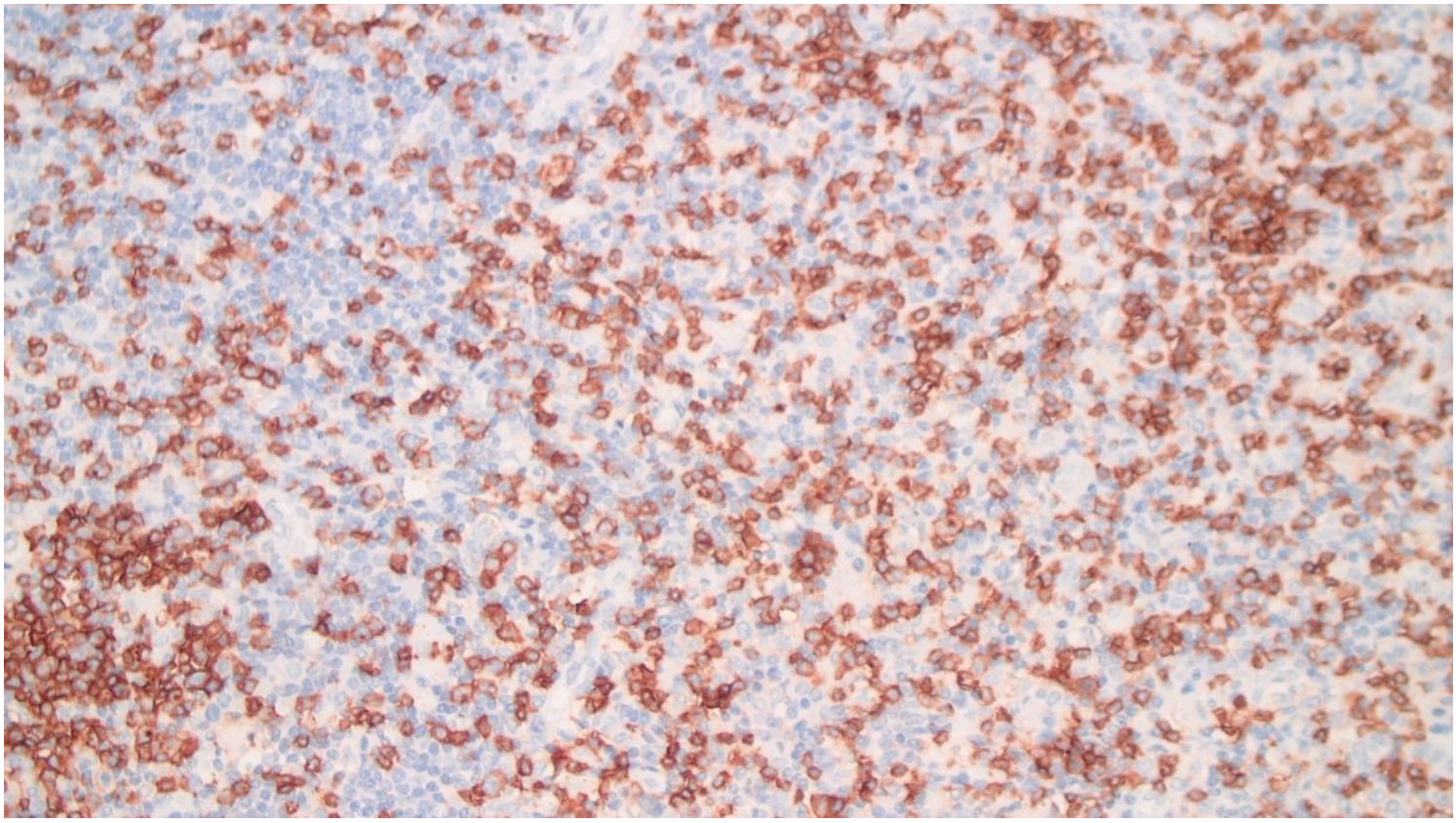

Figure 8

Proliferating CD8 positive T cells in the paracortical zone.

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