NYU Langone Health

DEPARTMENT OF PATHOLOGY

Case of the Week

Hematopathology: Nodular Sclerosing Hodgkin's Lymphoma

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History

The patient is a female in her mid-30's. She complained of fever, night sweats, and rapid weight loss ("B symptoms"). A CT scan of the abdomen and pelvis revealed an anterior mediastianl mass. She was sent to the OR for resection. A frozen section and touch preparation are performed intraoperatively.

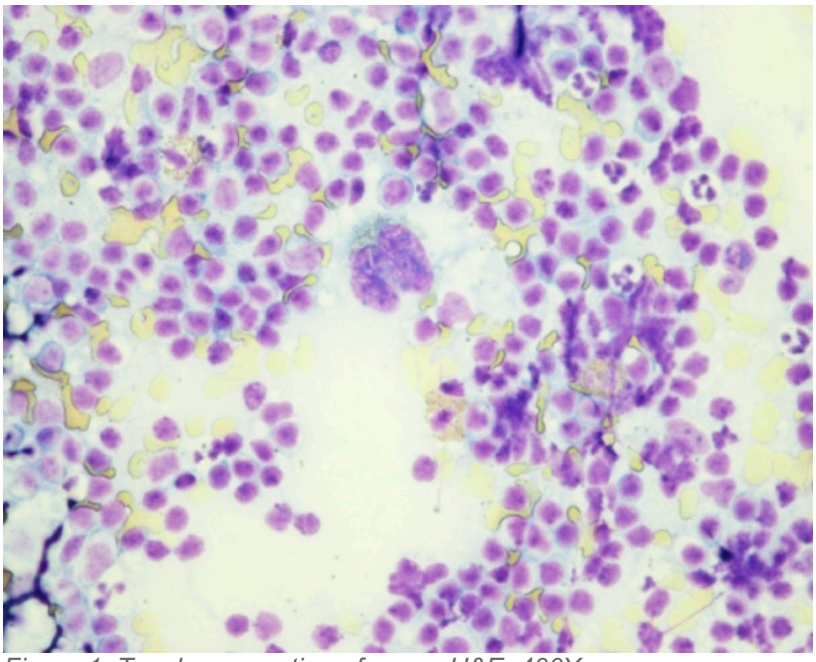

Figure 1: Touch preparation of mass, H&E, 400X

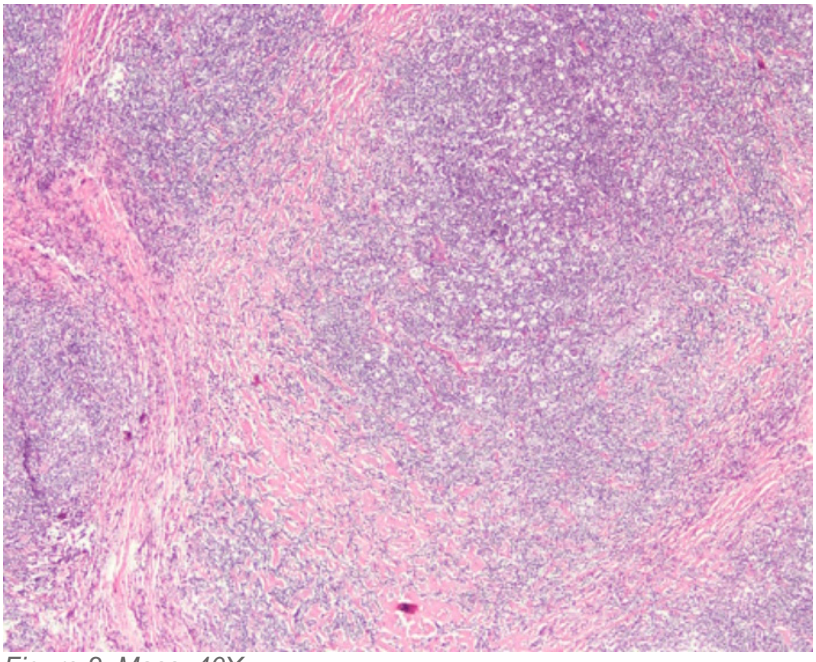

Figure 2: Mass, 40X

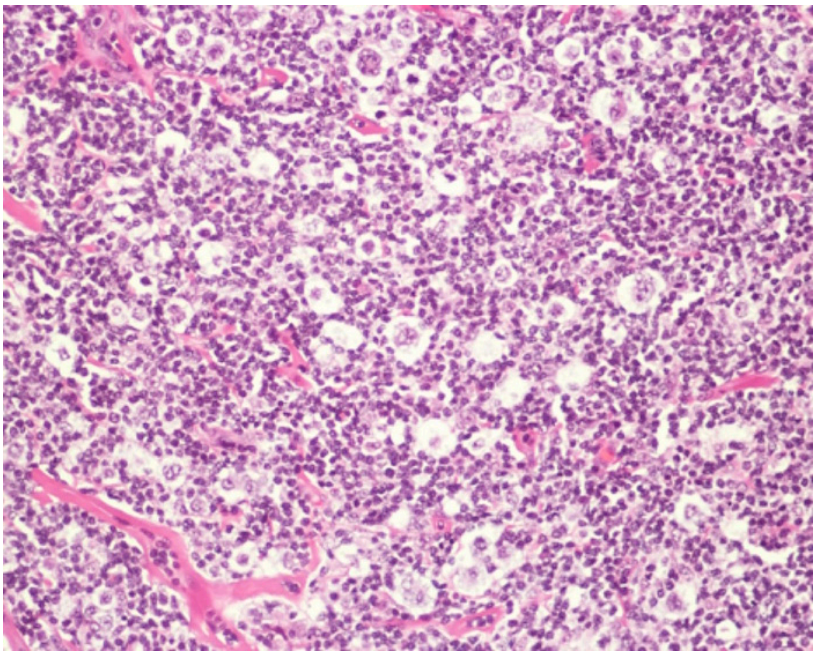

Figure 3: Mass, 200X

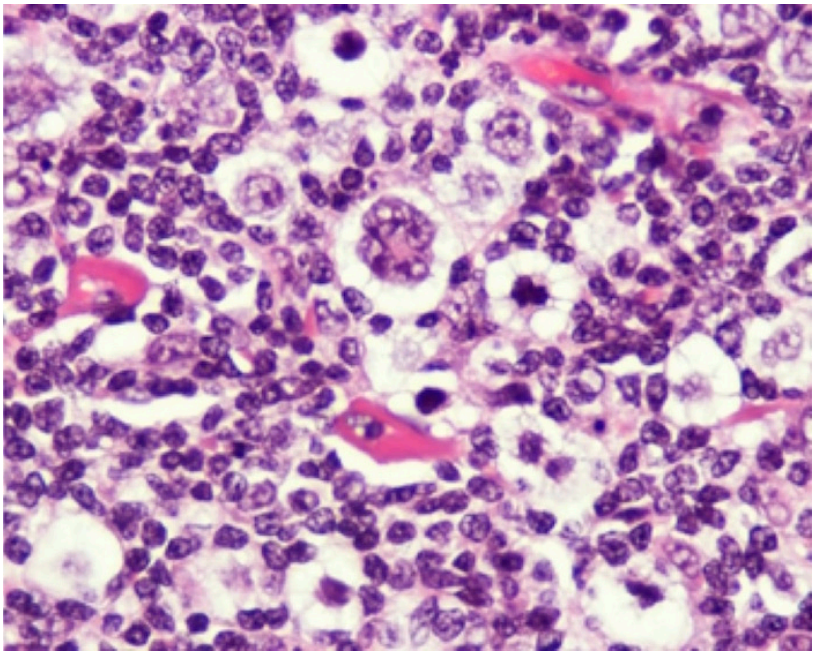

Figure 4: Mass, 400X

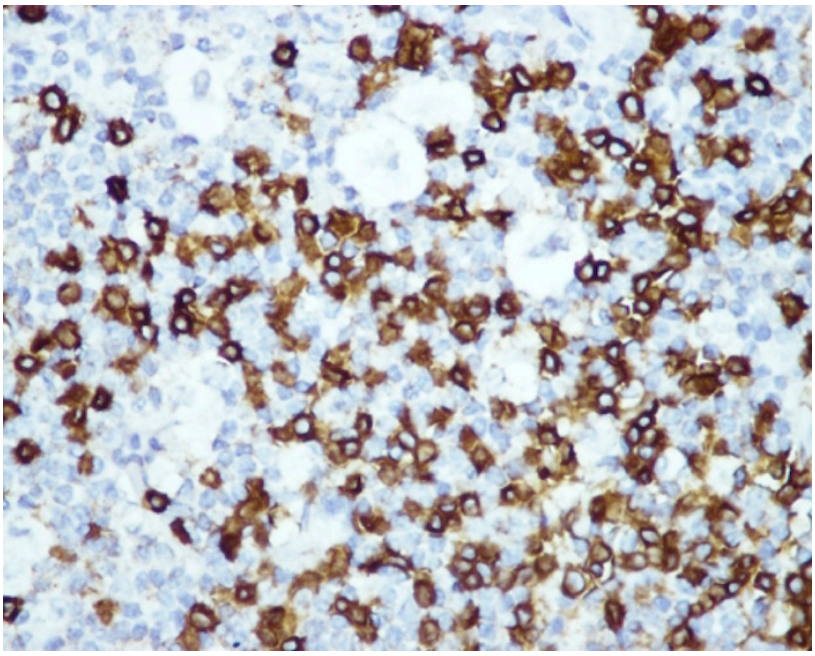

Figure 5: CD20, 400X

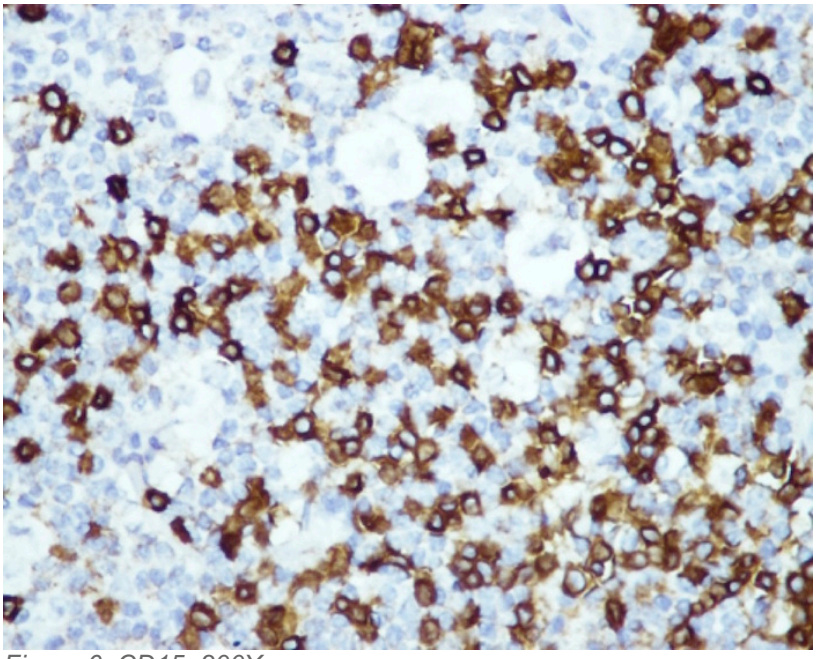

Figure 6: CD15, 200X

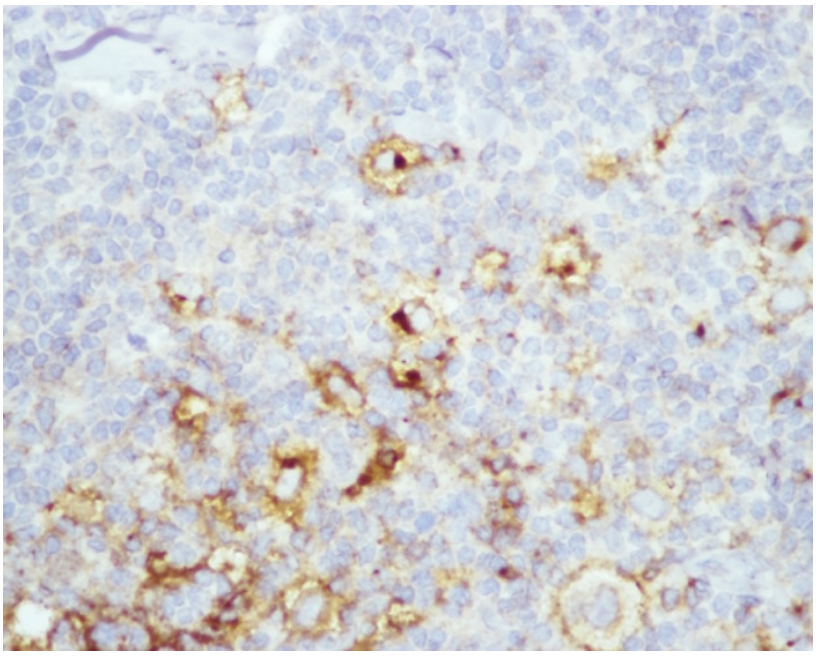

Figure 7: CD30, 400X

Figures 1-7

Figure 1: A touch preparation shows a cellular lesion, consisting predominantly of benign appearing inflammatory cells, including lymphocytes, neutrophils, and eosinophils. There are occasional giant cells showing bi- and multinucleation, clumped hyperchromasia, and conspicuous nucleoli.

Figures 2-4. Fig. 2: On low power, a densely cellular nodular architecture with fibrous septae is seen. The nodules are punctuated by numerous pleomorphic cells. Fig. 3,4: These cells exhibit annular circumferential clearing, a formalin fixation artifact characteristic of this tumor. Of note, there is also "popcorn" like vacuolation in these tumor cells.

Figures 5-7 Fig. 5: Immunohistochemical stain for CD20 and CD3 (not shown) highlights the B and T lymphocyte, respectively.

Fig. 6,7: The large cells are positive for CD15 and CD30 (membranous pattern). Other immunohistochemical stains performed: ALK and CD45 are negative.

Diagnosis

Nodular sclerosis Hodgkin lymphoma.

Discussion

Introduction
The patient is a 37 year old female who presented with B symptoms. A clinical differential diagnosis for this presentation would include acute HIV infection, malignancy, and drug reaction. Imaging studies reveal an anterior mediastinal mass. Pathology received a 4.5 cm, firm mass, with a nodular cut surface. Based on characteristic morphology and confirmatory immunohistochemistry, a diagnosis of Classic Hodgkin Lymphoma, nodular sclerosing variant, was rendered.

There are four types of Classic Hodgkin Lymphoma. All are characterized by a proliferation of CD15+, CD30+, CD45- Reed-Sternberg (HRS) cells, which are negative for B and T cell markers, which will highlight the non-malignant reactive lymphocytes. These cells are usually surrounded by reactive inflammatory cells which may include lymphocytes, neutrophils, eosinophils, plasma cells, and histiocytes. They can have two or more nuclei and are sometimes described as “owl eye.”

Nodular sclerosing Hodgkin Lymphoma is the most common subtype (60 to 70% of cases). It is more common in high socioeconomic status populations, with an equal male and female incidence. Forty percent will have B-symptoms, as did the current patient.

Mixed cellularity Hodgkin lymphoma is the second most common subtype (~25%). It presents in the immunocompromised and those in developing countries, and favors men. It is aggressive but highly curable. B symptoms are frequent. Microscopically there are typical HRS cells admixed with a variable inflammatory background (eosinophils, histiocytes, neutrophils, plasma cells). There may be epithelioid granulomas in EBV+ cases.

Lymphocyte-depleted Hodgkin lymphoma makes up ~4% of cases, carries a poor prognosis, is associated with HIV and affects younger men. 90% of cases have subdiaphragmatic involvement. Organomegaly, marrow infiltration, peripheral, and retroperitoneal involvement are common. Histologically it can be of a “diffuse fibrosis” form, with disorderly connective tissue and rare HRS cells, or of a “reticular” form with numerous bizarre HRS cells. Theses must be differentiated from anaplastic large cell lymphoma, DLBL, and others.

Lymphocyte-rich classic Hodgkin lymphoma has a 2:1 male predominance, lacks B symptoms and boasts the highest cure rate. It lacks neutrophils and eosinophils. It’s HRS cells can resemble those of nodular sclerosing Hodgkin Lymphoma or popcorn cells of lymphocyte predominant Hodgkin lymphoma. It is easily confused for the latter.

Microscopic findings/ Immunohistochemistry:
The touch preparation showed tumor giant cells with a mixed inflammatory infiltrate. On H&E low power magnification, architecture consisted of large, round, densely but heterogeneously cellular areas surrounded by thick, pink, fibrous septations. These nodules were punctuated with frequent multinucleated giant cells consistent with Lacunar Hodgkin Reed-Sternberg cells of Classic Nodular Sclerosing Hodgkin Lymphoma. CD3 and CD 20 highlight the mixed populations of lymphocytes. CD15 and CD30 stain the HRS cells. ALK and CD45/LCA were

negative, making anaplastic large cell lymphoma and DLBCL unlikely. CD45 negativity eliminates lymphocyte predominant Hodgkin lymphoma.

Genetics
Although the IgH locus at 14q32 is involved in Classic Hodgkin Lymphoma (CHL), recurrent translocations typical for non-Hodgkin lymphoma NHL are absent. Because of the small percentage of neoplastic cells in involved tissues and the difficulties in growing them in culture, cytogenetic examination of CHL has proved difficult. Hyperpoloidy is uniformly present in CHL. Comparative genomic hybridization of isolated RS cells after random genomic amplification has been used to quantify gains and losses of chromosomal material, leading to the identification of a commonly amplified region on 2p13 containing the REL oncogene. REL encodes a part of the Rel-A/NF-κB complex, which is constitutively activated in CHL.[1,2]

NF-κB and AP-1 transcription factor proteins are constitutively active, driving the proliferation of HRS cells and helping them evade apoptosis. Deletions or inactivating mutations of IκBα gene, an inhibitor of NF-κB, as well as amplifications of the REL oncogene are also thought to play a role.[3,4] Also, aberrant activation of several tyrosine kinases cause constitutive activity of Notch 1, PI3K/AKT, MAPK, STAT3, and STAT6 pathways.[5]

Management
Classic Hodgkin Lymphoma is treated with chemoradiation. The regimen consists of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD). The number of cycles and length of treatment is based on clinical stage and prognostic indicators such as presence of B symptoms, ESR, and tumor burden. For relapsed, refractory, or late stage disease, the BEACOPP (belomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen is used. This is complicated by frequent infections, the need for Nuepagen and bone marrow transplants.

References

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3. Martin-Subero JI, Gesk S, Harder L, et al: Recurrent involvement of the REL and BCL11A loci in classical Hodgkin lymphoma. Blood 2002; 99: pp. 1474-1477

4. Emmerich F, Meiser M, Hummel M, et al: Overexpression of I kappa B alpha without inhibition of NF-kappaB activity and mutations in the I kappa B alpha gene in Reed-Sternberg cells. Blood 1999; 94: pp. 3129-3134

5. Renne C, Willenbrock K, Kuppers R, et al: Autocrine- and paracrine-activated receptor tyrosine kinases in classic Hodgkin lymphoma. Blood 2005; 105: pp. 4051-4059