

## SYNCYTIAL VARIANT OF NODULAR SCLEROSING HODGKIN LYMPHOMA

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### ABSTRACT

*We report the case history of a 31-year old woman with a rare morphologic form of nodular sclerosing Hodgkin disease (NSHD) termed "syncytial variant." Its histologic features mimic metastatic carcinoma, thymoma, melanoma, non-Hodgkin lymphoma and germ-cell tumor. Antigens expressed on Reed-Sternberg cells, the hallmark of Hodgkin disease, and other neoplastic cells were screened to determine the correct diagnosis. This patient demonstrates the importance of using specific immunohistochemical techniques to clarify the diagnosis of NSHD of the "syncytial variant" subtype.*

The incidence of mediastinal disease in adult patients with non-Hodgkin lymphoma is between 15% and 25%, whereas primary mediastinal lymphoma occurs in ~9% of non-Hodgkin lymphoma patients (1). In contrast, patients with Hodgkin lymphoma are more likely to have mediastinal involvement. Filley et al reported that among 164 patients with Hodgkin disease, 52% had lymphoma involving the mediastinum (2). Given the high degree of potential mediastinal involvement in Hodgkin disease patients, accurate diagnosis of this entity is paramount for proper treatment.

Within the four histological types of Hodgkin disease, nodular sclerosing Hodgkin disease (NSHD) is histologically identified by the presence of varied numbers of both Reed-

Sternberg (RS) and lacunar cells. According to Strickler et al (3), when large numbers of these cells are present, they often are arranged in sheets or cohesive clusters. The manifestation of such cell clustering has been termed "syncytial variant" NSHD by these authors, in agreement with the initial classification proposed by Butler (4).

The diagnosis of syncytial variant NSHD is difficult because of strong morphologic similarities to metastatic carcinoma, metastatic melanoma, thymoma, non-Hodgkin lymphoma, or germ cell tumors (3,5). Previous reports have emphasized that histologic evaluation alone of suspected Hodgkin disease can be misleading (3,5).

The following patient demonstrates the importance of using specific immunohistochemical techniques to clarify the differential diagnosis surrounding NSHD of the "syncytial variant" subtype.

### CASE REPORT

A 31-year old Hispanic woman was admitted with shortness of breath, productive cough, wheezing, and pleuritic chest pain. She had a history of intermittent low-grade fever, weight loss of 10 pounds, and changes in vocal function. She smoked one-half pack of cigarettes a day for the past 15 years and occasionally used cocaine. In addition, she had a history of bronchial asthma and a schizo-affective disorder treated with sertraline.



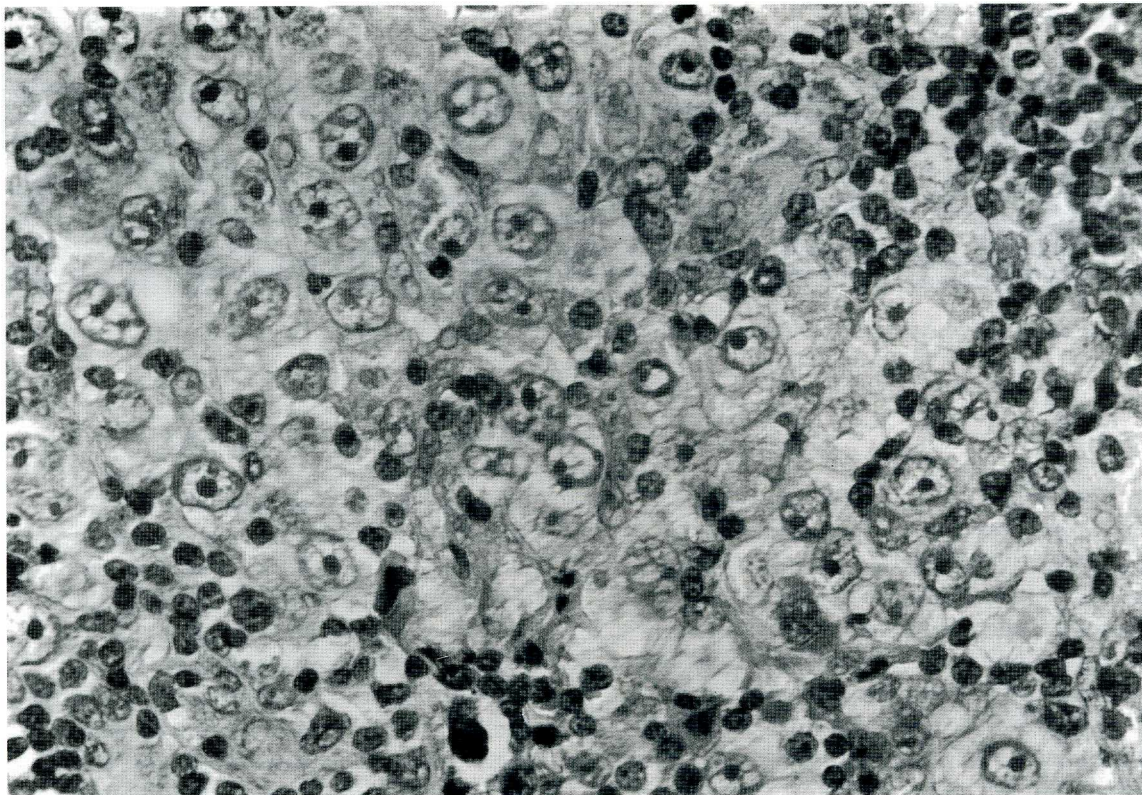


Fig. 1. The "syncytial variant" of nodular sclerosing Hodgkin lymphoma demonstrating sheets or clusters of large mononuclear or Reed-Sternberg-like cells that lie in the background of lymphocytes. (Hematoxylin and Eosin, x 400).

The physical examination was unremarkable. Chest radiograph and CT scan revealed bilateral hilar lymphadenopathy with an infiltrate in the upper lobe of the right lung and fullness of the retrosternal space. Two fiberoptic bronchoscopic examinations showed no abnormalities.

A right posterolateral thoracotomy was performed to obtain tissue for diagnosis. There were multiple enlarged, firm lymph nodes in the anterior and middle mediastinum, the largest measuring 3x3 cm. In addition, the right upper lobe and medial aspect of the middle lobe were thickened and appeared to be involved with disease. Frozen sections confirmed malignant lymphoma. The patient underwent middle mediastinal lymph node biopsy, and resection of the diseased portion of the right upper lobe. The postoperative course was uneventful.

The histopathology of the excised lymph node and lung tissue revealed nodular sclerosing Hodgkin lymphoma of "syncytial variant" type (Fig. 1). On immunohistochemical analysis, the tumor cells showed positive reaction with CD<sub>15</sub> (Leu-M<sub>1</sub>), CD<sub>30</sub> (Ki-I), but no reaction was detected with keratins (AE<sub>1</sub>), CAM 5.2, CEA (carcinoembryonic antigen), S100 protein or placental alkaline phosphatases (Fig. 2). Flow cytometric analysis of the excised lymph node showed mixed population of lymphocytes with no monoclonality, which further supported the morphologic and immunohistochemical findings of Hodgkin lymphoma.

The patient receiving an alternating chemotherapeutic regimen of mechlorethamine (nitrogen mustard), vincristine (Oncovin), procarbazine, and prednisone (MOPP) with adriamycin, bleomycin,



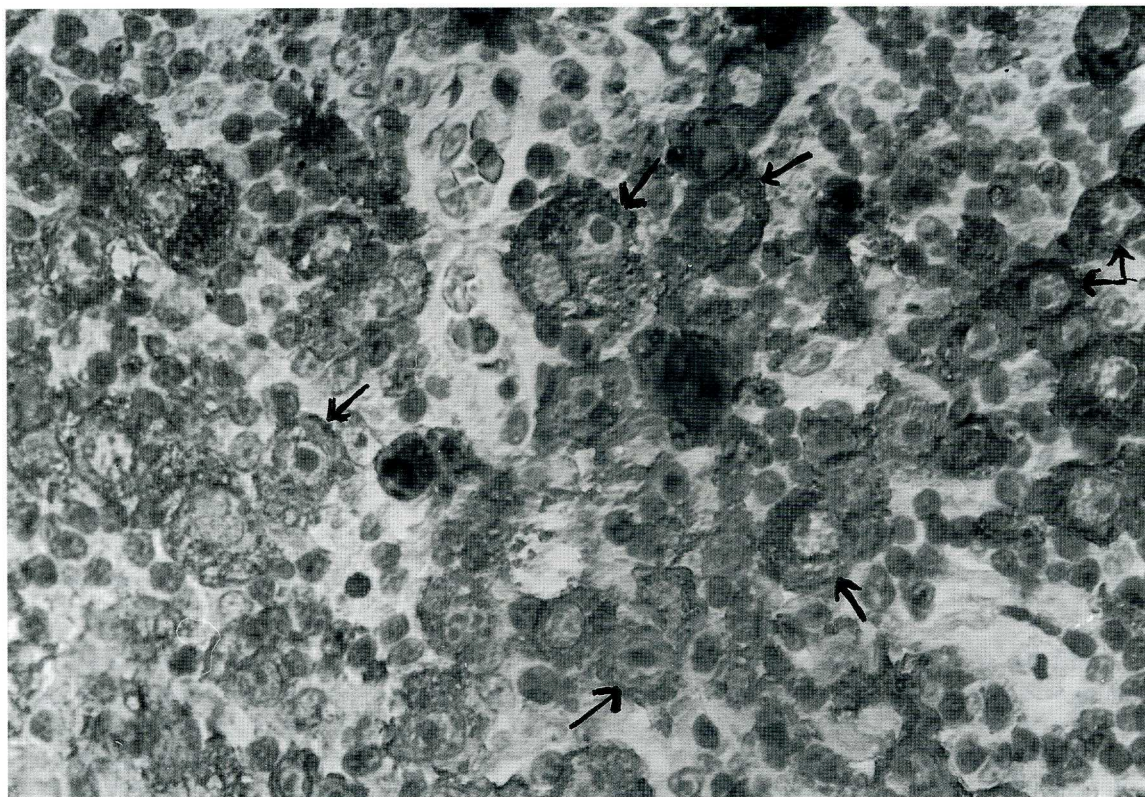


Fig. 2. Diffuse cytoplasmic staining of Reed-Sternberg variants with CD15 (Leu-Mi) immunomarker (arrows).

vinblastine, and dacarbazine (ABVD). Bone marrow biopsies, conducted postoperatively, were negative for lymphoma. There has been no further evidence of distant lymph node or organ involvement.

#### DISCUSSION

Hodgkin lymphoma is identified histologically when Reed-Sternberg (RS) cells are found within lymphatic tissue. These large cells can exist as a number of distinct morphological entities, frequently containing bilobed or multi-lobed nuclei and prominent inclusion body-like nucleoli. RS cells, however, are not limited to Hodgkin disease, but may occasionally be seen in patients with infectious mononucleosis and non-Hodgkin lymphoma (6).

Nodular sclerosing Hodgkin disease, the most common type of Hodgkin disease in

developed countries, is diagnosed by the presence of lacunar cells, RS cells, and bands of collagenous fibrosis; at least two of these features are required for diagnosis (7). The defining nature of NSHD is the presence of broad, parallel bands of interconnecting collagen fibers that originate in the capsule of the lymph node, thereby separating the affected node with discrete nodules (8).

A mixture of both RS cells of the classical mononuclear variety and unusual multinucleated forms is the hallmark of the "syncytial variant" of NSHD (7) as first observed in eight patients by Banks (9) in 1981. An additional characteristic feature is cohesive sheets of lacunar-like cells that bear a strong morphologic resemblance to various forms of neoplasia, including undifferentiated carcinoma, malignant histiocytosis, and non-Hodgkin malignant lymphoma (9).



**TABLE 1**  
**Immunohistochemical Markers Characteristic of Hodgkin Lymphoma**  
**(Syncytial Variant) Compared with Other Tumors of Similar Histopathology**

	CD15 (Leu-MI)	CD30 (Ki-1)	CD20 (UCL-1)	Cyto Keratin	CEA <sup>1</sup>	S-100	PAP <sup>2</sup>
Hodgkin Lymphoma	++	+	-	-	-	-	-
Non-Hodgkin Lymphoma	-	-	+	-	-	-	-
Metastatic Carcinoma	-	-	-	+	-	-	-
Thymoma	-	-	-	+	+	-	-
Melanoma	-	-	-	-	-	+	-
Germ Cell Tumors	-	-	-	-	-	-	+

1=Carcino-embryonic antigen; 2=Placental alkaline phosphatase

Strickler et al (3) utilized a group of immunochemical stains to confirm the presence of NSHD. RS cells express the Leu-M1 antigen, a marker for these cells. As reported, 13 of the 18 tissue samples obtained from the patients studied exhibited positive Leu-M1 antibody staining; the lack of keratin-immunoreactivity excluded metastatic carcinoma, thymoma, and germ cell tumors. The possibility of metastatic melanoma was nullified by positive Leu-M1 staining and negative staining for the S-100 protein marker. Further confirmation of HD was revealed by a characteristic pattern of staining for the leukocyte common antigen PD7/26 (3). The immunohistochemical features applied by us in the differential diagnosis of syncytial variant of Hodgkin lymphoma are shown in *Table 1*.

In a separate study, Ben-Yahuda-Salz and colleagues (5) identified the syncytial variant of NSHD in eight of 58 patients (age range, 16 to 36 yr; median age, 25) studied. These authors pointed out that 7 of the 8 patients (87.5%) exhibited severe class B (systemic) symptoms and had advanced state III or IV disease. Of patients with NSHD (N=50), those with syncytial variant NSHD

(n=8) had a statistically significant increase in mediastinal size, to more than 33% of total chest diameter ( $p < 0.0001$ ). Furthermore, four of the eight patients with syncytial variant NSHD required urgent treatment of life-threatening airway obstruction.

Given the severity of syncytial variant NSHD and the young age of the patients, accurate identification of the entity is paramount. In light of the complexities surrounding the diagnosis of syncytial variant NSHD, Brazier and Cyama recently reviewed the mistaken diagnosis reported within the classification of NSHD (10). Such diagnostic errors are avoided by using a select group of antibodies to screen for cell surface antigens specific to RS cells (Leu-MI), various T cell antigens (T11, Leu 9, T4, T8), epithelial cells antigen (cytokeratins), and S-100 proteins (11). In addition to the differential staining patterns for these antibodies, histologic clues suggestive of other unrelated conditions also deserve careful consideration. The presence of rare spindle-shaped neoplastic tumor cell infiltration into the lymph nodal sinuses, phagocytosis of neutrophils and extreme anaplasia in suspect RS cells, should raise suspicion of other possible malignancies.

## SUMMARY

The syncytial variant of nodular sclerosing Hodgkin lymphoma occurs in young patients who usually exhibit advanced disease and severe systemic symptoms. To date, long-term survival and clinical response rates are inconclusive, given the paucity of reported cases and short follow-up periods for most patients. Histologically, NSHD can be mistaken for metastatic carcinoma, germ cell tumors, thymoma, non-Hodgkin lymphoma, and melanoma, posing a challenge to the clinician. Careful evaluation including use of immunomarkers for CD15 (Leu M1 antigen) is considered reactive positive if any of three patterns (13) are seen: (a) Golgi or juxta-nuclear localization of the reaction product, (b) cytoplasmic localization, and (c) strong cell membrane localization (ring staining). The presence of any of these staining patterns and the lack of expression of keratins and S-100 protein help identify this entity.

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