Leukemoid Reaction

A Diagnostic Clue in Metastatic Carcinoma Mimicking Classic Hodgkin Lymphoma

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We report on 2 patients who were initially suspected to have classic Hodgkin lymphoma because of lymphadenopathy and the presence of Reed-Sternberg-like cells. Both patients had an associated leukemoid reaction (using a threshold leukocyte count of 50,000/μL) and were eventually diagnosed with metastatic carcinoma. Disseminated carcinoma can mimic Hodgkin lymphoma clinically, radiologically, and histologically. Reed-Sternberg-like cells may be found in carcinomas, and they represent a particularly challenging diagnostic pitfall for the unwary. When these cells lead to a suspicion of Hodgkin lymphoma, the presence of a leukemoid reaction should prompt the pathologist to question the diagnosis. MISdiagnosis can be avoided by the use of cytokeratin whenever a leukemoid reaction is present in a suspected case of Hodgkin lymphoma.

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Reed-Sternberg (RS) cells, when found on a background of lymphocytes, plasma cells, and eosinophils, suggest a diagnosis of classic Hodgkin lymphoma. However, RS-like cells can be seen in carcinomas and can lead to misdiagnosis. Leukemoid reactions (using a threshold leukocyte count of 50,000/μL) are relatively far more likely to be encountered in the setting of metastatic carcinoma rather than in Hodgkin lymphoma. We report here on 2 patients with leukemoid reactions in a setting of disseminated malignancy. The presence of RS-like cells histologically led to an initial impression of Hodgkin lymphoma, but both patients were eventually diagnosed as having metastatic carcinomas.

REPORT OF CASES

Case 1

A 78-year-old man presented with cough, shortness of breath, and weight loss for several months. Radiologic investigations revealed a 5-cm right lung mass with enlarged hilar and mediastinal lymph nodes. Cytologic examination of brushings obtained at bronchoscopy revealed RS cells (Figure 1), suspicious for classic Hodgkin lymphoma. Staging for Hodgkin lymphoma was performed. Complete blood count at diagnosis revealed a total leukocyte count of 52,000/μL, with 92% neutrophils, 3% bands, 4% lymphocytes, and 1% monocytes. There was no middle bulge or basophilia. Bone marrow biopsy revealed a hypercellular marrow with no evidence of malignancy. The hematologic picture was suggestive of a leukemoid reaction. Computed tomographic scan of the abdomen showed bilateral 5-cm hypodense adrenal masses lacking contrast enhancement (Figure 2). The patient developed superior vena cava syndrome for which radiotherapy was planned. In view of the need for a definitive diagnosis prior to radiotherapy, a bronchoscopic biopsy was performed, which showed a non–small-cell carcinoma with RS-like cells. The atypical cells stained positively for cytokeratin (CK) and negatively for CD15 and CD30. The diagnosis was revised to carcinoma of the lung with metastases to the adrenals. The patient died 4 weeks after diagnosis despite treatment with carboplatin, paclitaxel, and radiation therapy.

Case 2

A 37-year-old man presented with worsening abdominal pain and a 50-pound weight loss during a 3-month period. Examination revealed left posterior cervical lymphadenopathy and hepatomegaly. Complete blood count at diagnosis revealed a total leukocyte count of 50,000/μL, with 94% neutrophils and without a middle bulge or basophilia, which is consistent with a leukemoid reaction. Computed tomographic scans of the abdomen revealed a right-sided abdominal mass, which appeared to be arising from the kidney, with involvement of the retroperitoneal lymph nodes (Figure 3). The clinicoradiologic differential diagnosis was lymphoma versus metastatic carcinoma. Excision biopsy of cervical lymph nodes showed extensive infiltration by dyscohesive sheets of large RS-like cells (Figure 4). The background consisted of neutrophils and occasional plasma cells. The histologic picture was considered suspicious for classic Hodgkin lymphoma. However, immunohistochemical stains showed the RS-like cells to be positive for pan-CK, CK CAM 5.2, and CK AE1/AE3 (focal). The cells were negative for leukocyte common antigen, CD20, CD3, CD30, and CD15. A diagnosis of metastatic carcinoma was made. The results of additional immunostains (CK7 and CK20 negative, vimentin positive) suggested a renal primary. The patient developed painful scrotal swelling, which was thought to be caused by progressive retroperitoneal adenopathy. Radiotherapy was administered to the retroperitoneum. Despite therapy with paclitaxel and carboplatin, the patient died 6 weeks after diagnosis.

COMMENT

The presence of RS-like cells in several conditions other than classic Hodgkin lymphoma is well documented in the literature.1–4 These conditions include several subtypes.
of non-Hodgkin lymphoma, carcinomas of the lung and breast, melanoma, thymoma, inflammatory myxohyaline tumor of distal extremities, infectious mononucleosis, and rubeola.1-4 The ability of metastatic carcinoma, in particular, to simulate classic Hodgkin lymphoma has been described previously.5 A cytologic or histologic diagnosis of classic Hodgkin lymphoma must be made only in the context of the appropriate cellular background (eosinophils, plasma cells, and small lymphocytes). The absence of this typical milieu should prompt confirmation of the diagnosis with a panel of immunohistochemical stains. The other situation in which immunohistochemistry becomes imperative is when large numbers of neoplastic cells are seen (such as in case 2), such that excluding the possibility of metastatic carcinoma, large cell non-Hodgkin lymphoma, or melanoma would be especially important. For these reasons, among several others, there is a widespread acceptance among hematopathologists of the need to confirm the diagnosis of classic Hodgkin lymphoma by immunohistochemistry in virtually all cases at the time of initial diagnosis.

Leukemoid reaction is defined as a reactive leukocytosis in excess of 50,000/µL.6 It is usually seen in response to infection, inflammation, or therapeutic agents such as growth factors and is less commonly caused by malignancy. Milder elevations in leukocyte count are common both in carcinoma and Hodgkin lymphoma. White cell counts in excess of 10,000/µL have been found in 14.5% of 227 patients with lung carcinoma7 and in 27% of 100 patients with Hodgkin lymphoma.8 However, although mild leukocytosis is common in Hodgkin lymphoma, leukemoid reactions are rare. In the series of 100 cases of Hodgkin lymphoma just cited, not a single case had a total leukocyte count of more than 50,000/µL.8 A review of the literature reveals only a handful of documented cases of Hodgkin-associated leukemoid reactions, most of which involve eosinophilia. On the contrary, leukemoid reaction is a well-documented paraneo-
plastic syndrome in primary lung cancer, with a frequency of 1.8% to 2.6%.7,9,10 A review of 47 cases of malignancy-associated leukemoid reaction revealed only 1 case associated with Hodgkin lymphoma, in contrast to 18 cases associated with lung cancer and 6 cases associated with renal carcinoma.9

Thus, although leukemoid reaction may occur in Hodgkin lymphoma, it is far more common in carcinomas. Reed-Sternberg-like cells constitute a well-known diagnostic pitfall, and their occurrence in a tumor causing a leukemoid reaction should be a clue that one is not dealing with classic Hodgkin lymphoma. This should prompt the use of CK in an immunohistochemical panel, helping to prevent potential misdiagnosis. It has been suggested that the appearance of leukemoid reaction in patients with carcinoma is a poor prognostic sign.7 The demise of both our patients soon after diagnosis appears to support this hypothesis.

References