Collision tumor-concurrent involvement of Virchow’s lymph node by Hodgkin’s disease and metastatic gastric adenocarcinoma

A Troisier’s sign and more?

Ibrahim S. Tillawi, FCAP, FASCP.

ABSTRACT

We describe the case of a 59-year-old Caucasian male who presented to the outpatient clinic with intractable hiccups, upper abdominal pain, repeated bouts of vomiting, and stiff neck. Physical examination revealed a cachetic male with pallor, with enlarged left supraclavicular (Virchow’s) lymph node and hepatosplenomegaly. Histologic examination of the excised lymph node revealed simultaneous presence of 2 malignant processes, nodular sclerosing classical Hodgkin’s lymphoma and metastatic adenocarcinoma. Subsequent investigations of the patient, revealed the presence of gastric adenocarcinoma. Although factors governing the coexistence and the possible order of appearance of the 2 pathologies in the present case remain unknown, attempts are made to elucidate the pathogenetic mechanisms that led to their existence.

Case Report. A 69-year-old Caucasian male was admitted for evaluation of intractable hiccups, upper abdominal pain, repeated bouts of vomiting, and stiff neck. Physical examination revealed a middle-aged male patient with cachexia, pallor, and enlarged left supraclavicular lymph node (approximately 4.5 cms). Vague abdominal rigidity was elicited in the epigastric region. The spleen was palpable and was approximately 6 cm in span. The liver enlarged to approximately 10 cm in the left mid-clavicular line with a nodular surface. No other masses were found. Laboratory tests revealed: hemoglobin 9.2 gm/dl [normal range (N) =13.5-17.5 gm/dl], hematocrit 27.2% (N=41-53%), white blood cell 17,200 /mm³ (N=4,000-10,000/
Collision tumor ... Tillawi

mm³), neutrophils 75%, lymphocytes 14%, monocytes 8%, eosinophils 1%, metamyelocytes 2%; platelets 461000/ ul (N=150,000-250,000); blood film revealed slight anisopoikilocytosis and leukoerythroblastic blood picture; alkaline phosphatase 460 U/L (N=30-120 U/liter); Gamma-GT 139 U/liter (N=1-94 U/liter); serum glutamic-pyruvic transaminase 25 IU/L (N=0-35 U/liter); serum glutamic-oxaloacetic transaminase 12 IU/L (N=0-35 U/liter); creatine kinase) lactate dehydrogenase (LDH) 196 IU/L (N=100-190 U/liter); total protein 6.1 gm/dl (N=5.5-8.0 g/dl); albumin 2.6 gm/dl (N=3.5-5.5 g/dl (50-60%); globulin 3.6 gm/dl (N=2.0-3.5 g/dl (40-50%); A/G ratio 0.6; heme occult test was positive. Serum protein electrophoresis revealed no bands; HIV-I test (twice) negative; carcinoembryonic antigen 471 (N=0-3.4 ng/ml). The excised left supraclavicular lymph node was composed of a soft tissue mass with rubbery consistency measuring approximately 4.5 x 4 x 3.5 cms. The cut surface was nodular, firm and bulging (Figure 1). The entire specimen was submitted for histopathologic examination. Sections of the lymph node showed total effacement of the architecture and replacement by a variable sized lymphoid nodules that are separated by polarizable connective tissue septae. The lymph node capsule from which the fibrous tissue septae originated from was markedly thickened (Figure 2). The nodules are composed mostly of small round lymphocytes with occasional scattering plasma cells and eosinophils. Within the lymphoid nodules several Reed-Sternberg variants (“Lacunar” cells) were identified (Figure 3). The lymphoid component comprised the majority of the lymph node sections. On close examination, a second and rather “subtle” minor component which consisted of an infiltrate

Figure 1 • Low power view of the cut section from the lymph node (fresh state). Note the markedly thickened outer fibrous tissue capsule, with a heterogeneously nodular composition brought about by the intervening fibrous tissue septae.

Figure 2 • A whole mount of one of the levels of the cut section of the lymph node, showing a markedly thickened outer capsule with highly irregular and non-uniformly distributed variable sized lymphoid nodules separated by polarizable connective tissue septae. (Hematoxylin and eosin; 2x magnification.)

Figure 3 • A high power view of one of the lymphoid nodules reveal small round lymphocytes with admixed plasma cells and eosinophils (not seen in this figure); a centrally placed Lacunar variant of Reed-Sternberg cell; these cells stained strongly with CD15 and CD30, but not with CD45. (Hematoxylin and eosin; 40x magnification.)

Figure 4 • High power view showing a malignant glands and crypts infiltrating with clear cut adherence to the lymphatic sinusoidal wall (left), and projecting into the lumen of the sinusoidal lymphatic space (right), such as, permeation. (Hematoxylin and eosin; 40x magnification.)
of metastatic neoplastic glands and crypts involving not only the lymphoid nodules, but tend to occur in the fibrous tissue septae and on occasion distend the sinusoids (Figure 4). These cells stained with CD15 and CD30 immunostaining, and failed to stain with CD45 (Figure 5), CD3, or CD20. Intense immunostaining of the metastatic neoplastic glands and crypts was observed with keratin and carcinoembryonic antigen (CEA) (Figure 6), mucicarmine and periodic acid Schiff stain were positive in the latter cell groups. The mixture of 2 components in the lymph node was not uniformly distributed, furthermore, in some sections, Hodgkin's lymphoma predominated with only rare microscopic fields showing metastatic adenocarcinoma. The fact that the metastatic neoplastic glands and crypts were very few made their identification initially rather difficult, as they were close mimics to the lymphovascular spaces. Immunostaining with keratin and CEA, revealed more of the metastatic cells than did the hematoxylin and eosin sections. The diagnosis of a collision tumor is composed of synchronous occurrence of Hodgkin's disease and metastatic adenocarcinoma was then made. An upper and lower gastrointestinal barium studies revealed marked diffuse narrowing of the gastric lumen. Head and neck CT scan was unremarkable. The CT scan of the abdomen revealed irregular thickening of the gastric wall, with retroperitoneal lymph node enlargement, and hepatosplenomegaly. The chest CT scan showed the presence of a moderate left pleural effusion. The pelvic CT scan revealed bilateral hydronephrosis due to masses involving both the ureterovesical regions. Bone scans revealed the presence of multiple widely scattered metastatic lesions. Bone marrow biopsy revealed simultaneous involvement by both Hodgkin's lymphoma (HL) and metastatic adenocarcinoma (MA), that showed similar histopathology and identical immunohistochemical staining properties to those seen in the lymph node. Gastric antral and fundic biopsies revealed the presence of infiltrating poorly differentiated (intestinal type) adenocarcinoma. Biopsies from the vesicoureteric region revealed metastatic adenocarcinoma. The patient was lost for follow up, as he was managed in another hospital.

**Discussion.** A collision tumor is defined as the concrescence of 2 histogenetically and topographically different neoplasms in one organ with little intermingling between the 2 component neoplasms and without areas of transition between the abutting separate primaries. A collision tumor also occurs when 2 separate carcinomas metastasize to the same lymph node or when carcinoma metastasizes to lymph nodes that contain malignant lymphoma. In cancer-to-cancer metastasis, the 2 histogenetically different neoplasms occur side by side with intermingling in one organ. The “host tumor” in the case under discussion, represents the lymphoproliferative disorder. The metastatic tumor may on occasion resemble the host tumor; hence, their separation requires sophisticated techniques. It is unknown whether metastasis of cancer-to-cancer is a random occurrence or is due to selective “lodging”, survival and growth within another malignant neoplasm. Troisier’s sign is the finding of a hard, enlarged, left supraclavicular (Virchow’s) lymph node, or sentinel lymph node, said to be pathognomonic of abdominal cancers, in particular gastric cancer. Rare exceptions of “early gastric cancer” reported from the Japanese literature in which some cases go on to develop early metastasis to Virchow’s lymph node without evidence of gastric cancer elsewhere. Hodgkin's disease
is unlikely to initially present (as the sole peripheral nodal manifestation) in the Virchow's lymph node without any accompanying contiguous involvement of the neighboring peripheral lymph nodes, usually, the ipsilateral upper deep cervical or the axillary groups of lymph nodes. The presence of 2 malignant processes co-existing in the same lymphatic area, is a highly unusual and uncommon phenomenon. From the etiological point of view, what could have led to the development of these 2 histogenetically unrelated neoplasms is either a chance association or common etiopathogenesis. It is postulated that this can be the result of 2 simultaneously operating different processes such as continuous proliferative stimulation and the presence of a common oncogenic factor, such as Epstein-Barr-Virus (EBV). Although we were unable to establish an unequivocal definite link between the 2 above mentioned neoplasms, the question remains, whether the 2 neoplasms were connected etiologically or was the synchronous occurrence of the 2 neoplasms merely fortuitous? The co-existence of non-uniformly distributed metastatic adenocarcinoma and Hodgkin's lymphoma in the same lymph node, as seen in this case, highlights the need for a thorough histopathological examination, the significance of analyzing subtle lymphoid architectural changes, and applying ancillary studies including immunohistochemistry and if need be molecular analysis in suspicious cases. From the etiological point of view, it has been universally accepted that EBV plays a role in the genesis of Hodgkin's lymphoma; recent information from the far East, such as Japan and Korea, implicate EBV in some patients with gene polymorphism to be susceptible for the development of gastric adenocarcinoma, which raises the question as to whether EBV played a role in the genesis of these 2 neoplasms. Some of the mechanisms that operate whenever metastasis to a lymph node of malignant tumors occur include the following: 1. efficiency of lymph nodes acting as filters influencing the microenvironment of the arriving tumor cells; 2. alterations in the adhesive interactions that normally govern the generation of T-cell immune responses, hence, slows the promotion of invasion and proliferation of the tumor cells in the lymph node; 3. histopathogenic alterations such as effects of the extracellular matrix will ultimately lead to the facilitation in the process of metastasis; 4. manipulation of the cytokine environment (growth factors), in a lymph node draining a primary epithelial tumor may in fact alter both the expression of cell adhesion molecules within the lymph node and the subsequent ability of the metastatic potential of the tumor cells arriving to the lymph node. Metastasis of carcinoma to lymphoproliferative process is rare as a result of the following: 1. obliteration of the lymphatic sinuses secondary to the sclerotic process, which is an integral property of host tumor and in this case, nodular sclerosing Hodgkin's lymphoma; 2. lymphoma produces cytokines that antagonizes the metastatic epithelial cells; this is of notable importance as Hodgkin's Reed-Sternberg cells express mRNA and proteins of various cytokines and cytokine receptors implying a predominant role for the cytokines in the pathophysiology of HL. The HL cells therefore, both express and produce large numbers of cytokines (with special reference to secretion of interleukin-6 by the Reed-Sternberg cells and by the histiocytes). In the report by Allal et al., concurrent interfollicular Hodgkin's disease and metastatic breast carcinoma in lymph nodes were noted in a female in a mastectomy sample; we share with these authors the same experience in being unable to identify the etiological factors influencing the coexistence of these 2 neoplasms. Fibrosis which is observed in nodular sclerosing Hodgkin's lymphoma, and incriminated in the process of secondarily obliteration of the lymphatic sinuses cannot be considered the cause as reported by Allal et al., as the variant of Hodgkin's lymphoma in their patient is interfollicular variant of mixed cellularity, which has no fibrosis as part of its pathogenesis. Multiple cancers involving the left supraclavicular lymph node as a diagnostic site is unusual. Of interest, the involvement of the lymph node in this patient was highly irregular and non-uniformly distributed; the majority of the lymph node was composed of Hodgkin's lymphoma, with only a minor component of metastatic adenocarcinoma. One may speculate that Hodgkin's lymphoma appeared in the lymph node prior to the appearance of metastatic adenocarcinoma, due to 1. the bulk of disease is in favor of HL, as it represents the majority; 2. the neoplastic crypts and glands “permeate the lymphovascular spaces of the lymph node, which are structures left patent and not involved by the sclerosis, and 3. Loss of the CD44 adhesion molecule and high microvessel density may play a significant role in the high incidence of lymph-vascular permeation and metastasis in carcinoma. Therefore thorough examination of a supraclavicular lymph node aided in the identification of the two malignancies. One may also argue whether fine needle aspiration biopsy (FNAB) can obscure the presence of a second malignancy if it were attempted in this patient prior to histopathological examination, encouraging thorough sampling rather than submitting representative sections.

The HL has been reported with other cancers, such as in a mesenteric lymph node of a patient undergoing surgery for colon cancer, breast, Kaposi sarcoma, hairy cell leukemia, the lymph node involved by thyroid cancer in a patient already treated for HL, or others. In these instances, there is at least a known...
underlying malignancy in the same patient prior to the final examination of the excised lymph node. In the above mentioned reports, the primary diagnostic tool was lymph node examination through radical surgical samples, (example, colectomy or mastectomy and others). The primary site and types of malignant neoplasms that metastasize to the left supraclavicular lymph node differ from those of the right supraclavicular lymph node. Tumors that usually metastasize to the Virchow’s (left supraclavicular) lymph node mostly originate from abdominal or pelvic metastatic neoplasms; that can be explained by the difference in the lymphatic drainage on both sides. Leukemias and lymphomas involved twice as much the right than they did the left supraclavicular lymph nodes; both right and left supraclavicular lymph nodes have equal chance of involvement by metastasis from the head and neck, thorax, breast, and skin. A prior history of cancer is available in 25-40% of patients with left supraclavicular lymph node metastasis. The time lapse between the diagnosis of the primary malignancy and the metastasis was between 6-18 months before the onset of the left supraclavicular lymphadenopathy; 82% of malignant nodes draining distant tumors were found to be lymph nodes on the left side. 15-17 Predisposition to the phenomenon of cancer to cancer metastasis include several postulations; these include, genetic susceptibility, advanced ages of the patient, alterations in the immunologic surveillance status (such as immunosuppression, which can be partly due to the “first” tumor), or exposure to common inducing agents. Staging patients with the phenomenon of cancer to cancer metastasis can sometimes be difficult; one important factor that may participate in this difficulty is missing, one of the “first” tumors, either due to the rarity of the entity of cancer to cancer metastasis, or due to occasionally close resemblance between the host and guest tumors (for example, neuroendocrine small cell carcinomas and small cell lymphoproliferative disorders), or when the diagnostic procedure used is FNAB, which itself involves some technically related false-negative yield.

References