Non-Hodgkin lymphoma and GIST: molecular pathways and clinical expressions

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Abstract: We report the case of a 64-year-old woman with a gastrointestinal stromal tumor and a diffuse large cell lymphoma. For this case, we conducted a literature review in an attempt to correlate these two neoplasms on a molecular basis. Diffuse large cell lymphoma is a subtype of non-Hodgkin lymphomas. The etiologic factor of these lymphomas is considered to be the mutations or allelic losses of the TP53 tumor suppressor gene and the overexpression of the bcl-2 oncogene. Gastrointestinal stromal tumors are mesenchymal tumors, which are typically defined by the expression of c-KIT (CD117) and CD34 genes in the tumor cells. Although there are references to dispersants in the literature about patients with both non-Hodgkin lymphoma and gastrointestinal stromal tumors, there is no common molecular pathway between these two diseases. In conclusion, there is no indication that these two neoplasms are relevant on a molecular basis.

Keywords: hematological malignacies, mesenchymal cells, gastrointestinal cancer

Introduction
A diffuse large-cell lymphoma (DLCL) of B-cell origin is a lymphoid neoplasm with diverse clinical manifestations. These neoplasms present as masses and grow rapidly, and cause symptoms when they infiltrate tissues or obstruct organs. These neoplasms can present either with B symptoms (fever, drenching night sweats, and weight loss) or pain when the lymphomatous mass enlarges rapidly.1 Gastrointestinal stromal tumors (GISTs) are relatively rare mesenchymal neoplasms of the gastrointestinal tract. GISTs develop from the Cajal cells and are the most common mesenchymal tumors of the gastrointestinal tract. They usually occur in the upper gastrointestinal tract, in areas such as the stomach; GISTs of the small bowel, esophagus, and rectum are less common.2 We report the case of a 64-year-old woman with a GIST and a DLCL. In this case, we conducted a literature review in an attempt to correlate these two neoplasms on a molecular basis.

Case presentation
A 64-year-old Caucasian female presented to the hospital with symptoms of infectious lung disease and weakness, with a medical history of rheumatoid arthritis, diabetes mellitus, and hypertension. She was accepted to the pulmonary department, where she was treated. During her treatment there, she was transfused with four units of packed red blood cells, and the computer tomography of her thorax revealed pathological lymph nodes of the mediastinum. Consequently, the patient was referred to the hematological department of our hospital with symptoms of fever starting 4 months before, drenching night sweats, weakness, and lung infection. She claimed a fever duration of 15 days, with three fever waves daily and...
a maximum body temperature of 40°C, followed by 10 days without fever. The physical examination revealed bulky axillary lymph nodes, and a biopsy of the left cervical lymph node was taken. The biopsy was positive for DLCL, including mediastinum B-cell lymphoma. The immunohistochemistry was CD20+, PAX-5+, CD79α+, CD30+, MUM1+, OCT-2+, LMP-1+, p53+, BCL2±/-+, cyclin D1—/-, CD45RA-, CD45+, CD79α+, CD30+, CD3-, CD5-, CD4-, CD8-, CD10-, BCL6-, AKL-1-, and EMA-. The patient’s hematological check showed 32% hematocrit, 10.6 hemoglobin, 90 mean corpuscular volume, and 29 mean corpuscular hemoglobin after transfusion. Anisocytosis and hypochromia were also found, as well as rouleaux formation. The blood count revealed 6800 white blood cells and 200,000 platelets. The biochemical analysis showed elevated uric acid, aspartate transaminase, and alanine transaminase levels. Her beta-2 microglobulin was 8.00 mg/L. Afterwards, a whole-body Gallium 67 scan and a computed tomography (CT) scan of her upper abdomen, lower abdomen, and retroperitoneal area were performed in order to define the stage of the disease. The stage was determined to be IIb, and the patient was started on a chemotherapy regimen of cyclophosphamide, hydroxydaunorubicin, vincristin, prednisolone, and rituximab. Nine circles of rituximab followed. After the ninth circle of chemotherapy, the patient was urged to have a thorax, upper abdomen, lower abdomen, and retroperitoneal area CT as part of her follow-up treatment.

The CT scan revealed a well-demarcated spherical mass that arose from the muscularis propria layer of the stomach in the level of the pylori, with overlying mucosal ulceration (Figure 1). The radiological image was compatible with that of a GIST, and the patient was accepted to the surgical department of our hospital. The patient complained of abdominal pain and discomfort, as well as belching. She was submitted for an esophagogastroduodenoscopy (EGD) and endoscopic ultrasonography. The EGD showed a polyloid mass with a 3-cm diameter, with ulceration on the mass located in the pyloric antrum, findings indicating a possible GIST (Figure 2). A tumor resection was decided upon and the patient was submitted for subtotal gastrectomy with Billroth II reattachment. The surgical specimen (Figure 3) was sent for histological examination. The histological examination confirmed the GIST diagnosis and the immunohistochemistry showed that the tumor was CD117+, CD34+, and focally positive for NSE and GFAP antigens. Additionally, it was negative for the α-SMA, myosin, desmin, S-100, CD3, and CD20 antigens. The tumor was fully resected and the lymph nodes were not infiltrated.

The 6-month follow-up included a thorax, upper abdomen, lower abdomen, and retroperitoneum area CT scan, as well as an EGD. The CT scans revealed a mild splenomegaly, while the other findings were normal. The endoscopy had no pathological findings.

**Discussion**

DLCL is a subtype of non-Hodgkin lymphomas. DLCLs represent a diverse spectrum of lymphoid neoplasms with variable clinical, histologic, immunophenotypic, cytogenetic, molecular, and genetic features, and they are of B-cell origin. According to the literature, B-cell-restricted markers (CD19,
CD20, CD22) are expressed in the majority of DLCLs. The most common activation antigens are expressed through the HLA-DR system. In contrast to the markers mentioned above, CD23 is less frequently expressed (0%–25%). The etiologic factor of these lymphomas is considered to be the mutations or allelic losses of the TP53 tumor suppressor gene (17p13.1). These changes are considered to be relevant with the evolution of these neoplasms. Another gene, the bcl-2 oncogene, is overexpressed in DLCLs. The bcl-2 is an important protein in the apoptotic pathway and is considered to have a critical role in drug resistance. The Bcl-2 protein is present in normal tissues, as well as in neoplastic ones, and high levels of this protein offer a survival advantage in B-cells by inhibiting apoptosis.

Mediastinal B-cell lymphoma is a recently identified subtype of diffuse large B-cell lymphoma. The pathogenesis of mediastinal B-cell lymphoma includes the activation of NF-κB pathways and the JAK2 genes. The NF-κB signaling pathway controls the cell death regulatory genes, resulting in the control of B-cell survival. There is a simultaneous decrease in the JAK signaling pathway. The two pathways mentioned above are a result of the increased expression of IL-13. The signal transducer and activator of transcription-1, tumor necrosis factor, and tumor necrosis factor receptor-associated factor are increased. Additionally, there is a nuclear translocation of the c-REL protein (Figure 4).

GISTs are mesenchymal tumors originating from the pluripotential mesenchymal stem cell, which is programmed to differentiate into the interstitial Cajal cell. GISTs are typically defined by the expression of c-KIT (CD117) and CD34 in the tumor cells. The c-KIT oncogene is located in...
Those drugs bind to a specific amino acid residue within the ATP binding pocket and in the activation loop, whereas sunitinib interacts with different amino acids within the ATP binding pocket. Additionally, disease progression is considered to be a result of c-KIT mutations in exons 13, 14, and 17, which decrease the tumor sensitivity to imatinib and additional chemotherapy. 

Although there are reports of dispersants in the literature of patients with coexisting non-Hodgkin lymphoma and GISTs, there is nothing to the authors’ knowledge indicating that there is a common molecular pathway between these two diseases.

Conclusion

Although there are references to dispersants in the literature about patients with both non-Hodgkin lymphoma and GISTs, there is no common molecular pathway between these two diseases. Genetic surveys have been done to try to establish a connection between lymphomas and GISTs, but there are no encouraging results. We believe that there should be further scientific interest on this field.

Authors’ contributions

M Karanikas, N Machairiotis, P Zarogoulidis, and A Stylianaki wrote the manuscript. N Lyratzopoulos, A Mitrikas, and A Polychronidis performed the surgery. N Courcoutsakis evaluated the radiographic findings. M Spanoudakis treated the patient while he was a member of the Hematology Department, University General Hospital of Alexandroupolis, Democritus University of Thrace, Alexandroupolis, Greece.
G Kouklakis, M Karanikas, N Lyrazilopoulos, A Mitrakas, and A Polychronidis treated the patient.

Disclosure

The authors report no conflicts of interest in this work.

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