Superior vena cava syndrome as an initial presentation of low-grade follicular lymphoma

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Superior vena cava (SVC) syndrome refers to a constellation of symptoms produced by the obstruction of blood flow through the SVC, resulting in symptoms of dyspnea, facial and upper-extremity edema, cough, chest pain, and dysphagia.[1] Malignancies represent 60%-85% of the etiologies of SVC syndrome. Cumulatively, lymphoma and lung cancer represent 95% of malignancy-related SVC syndrome etiologies, with non-small-cell lung cancer (NSCLC) reported in about 50% of cases, small-cell lung cancer (SCLC) in about 25%, and non-Hodgkin lymphoma (NHL) in 10 % of all cases.[1,2]

NHL is the fifth most common malignancy in the United States. It has several histopathological subtypes, the most common of which is follicular lymphoma (FL), a common indolent lymphoma. The estimated incidence of FL is 3.18 cases per 100,000 people in the United States,[3] with incidence generally increasing with age (median age at diagnosis, 60 years).[4]

The pathogenesis of follicular lymphoma has been linked to t (14:18), which results in overexpression of B-cell lymphoma/leukemia 2 (BCL2). Typically, this lymphoma manifests as intermittent peripheral lymphadenopathy that involves the cervical, axillary, inguinal, and femoral groups. Hilar and mediastinal lymph nodes may also be involved. A minority of patients – about 20% – will present with classic B symptoms, which include fever, night sweats, and unintentional weight loss. The initial presentation as a mediastinal mass or SVC syndrome is extremely rare. This case report will highlight a novel case of SVC syndrome as an initial presentation of a low-grade, Ann Arbor Stage III, follicular lymphoma.

Case presentation

A 48-year-old man with a past medical history of atrial fibrillation, presented to the emergency department with a history of progressively worsening dyspnea and declining exercise tolerance during the previous 4 weeks. This was preceded by an approximately 6-week history of nasal congestion, which was initially unresponsive to topical steroid therapy.

Further history was significant for 1 week of early morning awakening with facial and neck edema, which improved with erect posturing, and facial plethora with leaning forward. At presentation, he admitted to pain on the right side of his neck and the right, posterior shoulder with paresthesia of his right hand. He also experienced an intentional weight loss of 15 lb over the months leading up to his presentation. Further review of systems was negative for fever, chills, night sweats, or chest pain.

The results of the physical examination revealed an afebrile man without acute respiratory distress. There was evidence of facial plethora with bilateral neck fullness, without jugular venous distension. The right lung fields revealed absent air entry in the mid and lower lung zones, with a stony dull percussion note in the corresponding lung zones. There was palpable bilateral axillary and right-sided inguinal lymphadenopathy. Laboratory investigations revealed D-dimer, 920 ng/ml (normal range, 0-500 ng/ml); hemoglobin, 15.5 g/dL (13.5-17.5 g/dL); white blood cell count, 7.2 x 10^3/uL (4.0- 11.0 x 10^3/μL); platelets, 320 x 10^3/uL (150-400 x 10^3/uL); uric acid, 6.2 mg/dL (normal range – male, 4.8-8.7 mg/dL), and lactate dehydrogenase 154 IU/L (98-192 IU/L).

A computed-tomography scan of the thorax

showed a large right-sided dominant mediastinal mass measuring about 13.0 x 12.9 x 18 cm, with significant left-sided tracheal displacement and marked narrowing of the SVC and right upper lobe pulmonary artery (Figure 1). A large right pleural effusion, with near complete collapse of the right lower lobe, and moderate-to-large pericardial effusions were present.

The patient underwent pericardocentesis, which yielded 800 ml of pericardial fluid. Flow cytometry of the fluid demonstrated a population of surface kappa-restricted CD5- CD10+ CD19+ CD20+ CD23+ CD38+ IgM- B cells, which was consistent with the involvement of a mature B-cell lymphoma. In addition, a pleural fluid analysis revealed lymphocytic effusion, suspicious for lymphoma. Fine-needle aspiration and ultrasound-guided core biopsy were subsequently performed on the mediastinal mass, which showed the presence of a low-grade follicular lymphoma with a diffuse pattern. The diagnosis of follicular lymphoma was supported by immunohistochemical studies (Figure 2), which showed neoplastic cells to be positive for CD20, CD79a, CD10, CD23, BCL-2, and BCL-6; and negative for CD3, CD5, CD43, and BCL-1, with a Ki-67 proliferation index of about 20%. These overall findings were consistent with a low-grade follicular lymphoma with a diffuse pattern.

The patient was diagnosed with Ann Arbor Stage III low-grade follicular lymphoma. He was treated with the R-CHOP regimen (rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone), with a significant clinical response.

Discussion

This case highlights the initial atypical presentation of an indolent lymphoma, a presentation that is often typical of aggressive lymphomas. We performed an extensive literature search using Medline via OVID, PUBMED, and the Cochrane databases, but found no published data on SVC syndrome as an initial presentation in low-grade follicular lymphoma. In one series, 36 of 915 patients with NHL presented with SVC syndrome. The histological types associated with SVC syndrome were diffuse large-cell in 23 patients, lymphoblastic in 12, and follicular in 1 patient. Overall, 7% of the patients with diffuse large-cell lymphoma and 21% of the patients with lymphoblastic lymphoma had SVC syndrome. The overall frequency of SVC syndrome in the 915 cases, excluding Hodgkin disease, was 36 (3.9%).[5]

Aggressive subtypes of NHL range from acute to subacute presentations with rapidly enlarging mass, and the prominence of B symptoms. Laboratory data usually support states of rapid cell turn over, as evidenced by elevated serum LDH and uric acid. Typical presentations of indolent lymphomas are characterized by an insidious onset
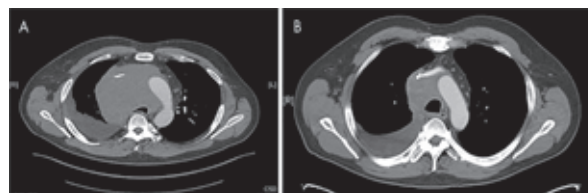
FIGURE 1 Computed-tomography scan of the thorax A, prechemotherapy and B, postchemotherapy.
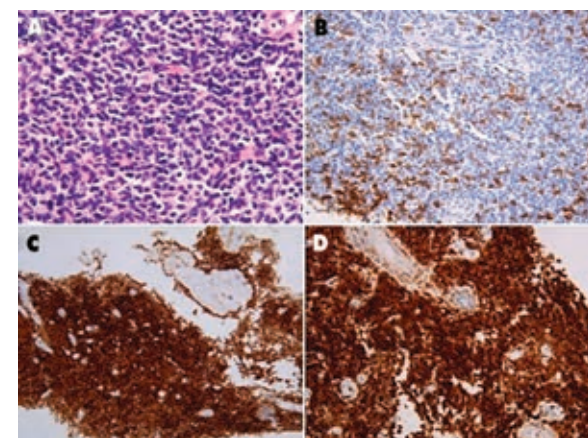
FIGURE 2 Histolopathology A, hematoxylin and eosin 400x; B, CD5 400x; C, CD10 200x; and D, BCL-2 200x.

with waxing and waning of peripheral lymphadenopathy.

This clinical presentation favored an aggressive lymphoma as supported by the large anterior mediastinal mass, SVC syndrome, malignant pleural, and pericardial effusions; however, a lack of B symptoms, in addition to histological and cytometric analysis, confirmed an indolent lymphoma. The patient was initially considered for enrollment in an Eastern Cooperative Oncology Group clinical trial in which patients received rituximab plus bendamustine combined, with or without bortezomib. However, after his initial presentation and discharge from hospital, he presented again 5 days later with recurrent pleural and pericardial effusions at which time therapy was promptly initiated with the combination regime of rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (R-CHOP). His response to this regimen was excellent after 6 cycles of therapy, with significant reduction in tumor burden radiographically and resolution of clinical symptoms.

Malignancy represents the most common etiology of SVC syndrome, occurring in about 90% of cases.[6,7] However, in the pre-antibiotic era, infectious etiologies, primarily (syphilitic aortic aneurysms and tuberculosis) were the leading causes. Less commonly observed benign conditions include fibrosing mediastinitis, fungal infection, postradiation fibrosis, and intravascular cath-

eter- and device-associated thrombosis. The incidence of SVC-syndrome associated thrombosis has risen with the significant increase in intravascular catheter placement, although overall incidence remains low.[6,8,9] NHL is the least common malignant cause of SVC syndrome, occurring in 2%-4 % of cases,[10] whereas Hodgkin lymphoma has been rarely identified.

The importance of the early recognition of SVC syndrome and definitive etiology is critical. Schraufnagel and colleagues, in a review of 107 cases of SVC syndrome, sought to evaluate whether there was a direct correlation between the onset of symptoms and the rate of complications and overall survival in these patients. They concluded that prognosis was dependent on the underlying etiology, with no support that SVC obstruction represents a radiotherapeutic emergency.[11]

True exceptions to this include cases of central airway obstruction, laryngeal edema, or coma secondary to cerebral edema, which is potentially life threatening and warrants the implementation of emergent therapeutic strategies such as stent placement and or radiation therapy. However, caution must be advised in the administration of radiotherapy before a histological diagnosis, because of the deleterious effects on the interpretation of histopathological specimens.

Loeffler and colleagues demonstrated this in a series of 19 patients who underwent emergent radiotherapy treatment for symptomatic mediastinal masses, 8 of the patients were not able to have a proven histological diagnosis at the time of biopsy.[12] The enormity of such scenarios rests on the impact of future treatment planning and the likelihood of using an empirical treatment regime, which may result in lower cure rates and higher rates of relapse. Currently, there are no evidence-based guidelines for the management of SVC syndrome, although with the advent of a proposed grading system as defined by Yu and colleagues, standardization of the approach to management of these patients may be likely in the future.[13]

In the current case, despite the patient's dramatic clinical symptoms at initial presentation, emergent therapy was appropriately not implemented before the establishment of a histopathological diagnosis. Symptoms of SVC syndrome typically develop over several weeks or longer, with no difference in outcome observed in the earlier implementation of therapy.[11]

This was supported in the current case as significant reduction in clinical and radiological tumor burden was noted at the completion of 6 cycles of R-CHOP therapy. If we had decided to empirically administer radiation therapy before biopsy, it would likely have had an impact on the interpretation of the biopsy specimens and ultimately, affect the choice of chemotherapy regimen which varies according to histological subtypes.

Conclusion

Malignancy is the most common etiological agent of SVC syndrome. Of the cases related to lymphoma, lymphoblastic and diffuse large B cell is the most common subtypes of NHL with follicular lymphoma only rarely identified. Initial management strategies should be geared toward definitive histological diagnosis[14] followed by the initiation of appropriate chemotherapy and/or radiation therapy. In addition, earlier use of endovascular stents in severely symptomatic patients should be considered, which has been supported in several trials.[15,16,17]

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