Spontaneous Regression of Classical Hodgkin Lymphoma: A Case Report and Review of the Literature

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Thomas Hodgkin first described Hodgkin lymphoma in 1832. Classical Hodgkin lymphoma (cHL) is a potentially curable hematologic malignancy with distinct histology, biologic behavior, and clinical characteristics. cHL is further divided into different subgroups, based on the appearance and immunophenotype of the tumor cells as well as the composition of the reactive background. Mixed-cellularity cHL represents 15–30% of cHL cases. The incidence rate of cHL is 2.8 per 100,000 men and women per year. It accounts for approximately 10% of all lymphomas and approximately 0.6% of all cancers diagnosed in the developed world annually.1,2 The improvement in 5-year survival is unmatched in the United States by any other cancer throughout the past 40 years. The overall 5-year relative survival rate is 84.7%.

cHL has a bimodal age distribution, with one peak in the 20s and 30s and a second peak after the age of 50.3 cHL of the elderly is defined as that occurring in patients older than 60 years.4 It is an uncommon disease. Older patients usually present with mixed cellularity histology and B symptoms. Progression-free and overall survival rates for elderly cHL patients are disproportionately inferior to those of younger patients. Survival rates for elderly patients with cHL are inferior to those achieved by younger populations. The 5-year overall survival rates for elderly cHL patients range from 40–55%, as compared to overall survival rates exceeding 80–90% for patients younger than 40 years.3,5-7

Spontaneous regression (SR) of cancer is the complete or partial disappearance of a malignant tumor without treatment or in the presence of therapy that is considered inadequate to exert a significant influence on neoplastic disease.8 SR can occur in cHL patients but is very rare. We report a case of SR of classical cHL in an elderly patient.

Case Report

An 86-year-old woman with no significant medical history was evaluated extensively for diffuse myalgia, proximal muscle weakness, skin rash, dry cough, and anemia. Her physical examination demonstrated multiple small cervical and inguinal lymph nodes bilaterally. She had an indurated, non-tender 3 × 3 cm lymph node in her left axilla. Her laboratory workup showed a white blood cell count of 2.9 × 10³/uL, a hemoglobin of 11.8 g/dL, a hematocrit of 33.9%, and a platelet count of 99 × 10³/uL. A full and extensive workup (including for antinuclear antibody, rheumatoid factor, anti–double-stranded DNA, anti-Ro [anti-SSA], anti-La [anti-SSB], antineutrophil cytoplasmic antibody, and human leukocyte antigen B27) was performed to rule out rheumatologic and autoimmune diseases, and all tests were negative. Upper and lower endoscopies, as well as a serum protein electrophoresis, were normal. Evaluation of the patient’s dry cough included a chest x-ray that showed a new hilar fullness. Subsequently, a computed tomography (CT) scan showed extensive lymphadenopathy in the chest, abdomen, and pelvis involving celiac, porta hepatis, splenic hilar, retroperitoneal, inguinal, pelvic, mesenteric, and peripancreatic nodes. The CT scan also showed splenomegaly of a moderate size (16 cm in greatest diameter), bilateral pleural effusions, and multiple irregular pulmonary nodules (Figure 1). An excisional biopsy of a left axillary lymph node showed classic cHL of mixed cellularity type (stage IV b), and a plan for treatment was initiated.

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Seven weeks later, 18-fluorodeoxyglucose positron emission tomography (PET)/CT was performed for staging purposes prior to the initiation of chemotherapy. It showed a marked decrease in the size and degree of lymphadenopathy in the chest, abdomen, and pelvis, with resolution of splenomegaly and pleural effusions as well as a marked decrease in the number of pulmonary nodules. Of note, the patient had not received any medications (eg, steroids, chemotherapy) or made any lifestyle changes. Subsequent follow-up imaging studies showed complete resolution of her lymphadenopathy (Figures 3 and 4). She continues to be in spontaneous remission 8 months after her initial diagnosis.

**Discussion**

The frequency of spontaneous regression of cancer has been estimated to be about 1 case per 100,000 patients. Approximately 20 cases are reported each year. The definition of spontaneous remission does not necessarily imply a spontaneous cure of the cancer, as it even applies to cases of incomplete or temporary regression of disease. It indicates that the tumor growth has stopped or reversed. Spontaneous regression is most commonly seen in hypernephroma, melanoma, neuroblastoma, leukemia, and non-Hodgkin lymphoma. This phenomenon is very rare in cHL. Left untreated, cHL has a 5-year
survival rate of less than 5%. Advanced cHL is usually treated with 6–8 cycles of anthracycline-based combination chemotherapy. We have identified 16 cases of spontaneous regression of cHL in the literature, with various follow-up periods ranging from several months to 8 years. Among these cases, 5 were of mixed cellularity type and occurred in children following measles infection. All of these patients still required treatment with chemotherapy following the regression.

The etiology underlying the development of spontaneous remission of cancer remains unclear. Review of the literature shows that the mechanisms that have been proposed to explain spontaneous remission of cancer include immunologic factors, concomitant infections, hormonal factors, elimination of carcinogens, surgical trauma of the primary tumor, induction of differentiation, and genetic factors.

The phenomenon is most often attributed to immunologic mechanisms. Such factors might have played a role in the natural regression of cHL in our particular patient. The constellation of other “systemic symptoms,” including severe myalgias, anemia, and weight loss, may be explained by an undiagnosed concomitant immunologic disease that could have intensified cellular and humoral immunity, thus leading to a spontaneous regression of the tumor. Our patient had no other identifiable triggers—such as infectious or inflammatory conditions—to explain the tumor regression, and, to our knowledge, she had not sought alternative therapy or used any medications surreptitiously. This case illustrates the role of natural immunity in fighting cancer. This type of observation may play an important role in developing targeted immunotherapies that could serve as treatment options for patients with cHL or other cancers.

References

Review

Classical Hodgkin Lymphoma and Spontaneous Regression

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Mohsen and colleagues describe an interesting case of an 86-year-old woman with biopsy-proven classical Hodgkin lymphoma (HL), mixed cellularity type, who initially presented with diffuse myalgia, pancytopenia, lymphadenopathy, splenomegaly, bilateral pleural effusions, and pulmonary nodules.1 She experienced near-complete regression of lymphoma shortly after diagnosis, before any tumor-specific therapy could be initiated. The authors hypothesize that the constitutional symptoms reported by the patient may reflect an underlying immunologic milieu contributing to this remission. Thorough testing was performed as part of the rheumatologic workup in order to rule out a concurrent underlying autoimmune disease due to the association between immunologic dysfunction and lymphomagenesis, as explained below.

Immunity and Lymphomas

Spontaneous regression has been described with relative frequency among various malignancies;2 and occurs more frequently in low-grade non-Hodgkin lymphoma (NHL).3,4 Our knowledge of spontaneous regression of cancer is derived primarily from case reports and case series. Sir William Osler recognized it in the early 20th century,5,6 and a detailed monograph of 176 cases of spontaneous regression postulated various explanations for this phenomenon, including immunologic, hormonal, pharmaceutical, surgical, infectious, and environmental causes. Notably, this report excluded leukemias, lymphomas, and squamous cell epitheliomas, as they were thought to “vary greatly in their growth.” Lymphoma pathogenesis is associated with immune dysregulation, particularly in patients with human immunodeficiency virus (HIV) infection and pharmacologic immunosuppression. The frequency of Epstein-Barr virus (EBV) involvement indicates the potential importance of immunity in the pathogenesis of these tumors. Acute EBV infection induces vigorous cellular immunity, and often results in latent infection of B cells.8 Patients with compromised EBV-specific T cells are at increased risk of B-cell proliferation with varying malignant potential. Immunosenescence in the elderly contributes to the development of age-related EBV-associated B-cell lymphoproliferative disorders, including HL.9 In post-transplant lymphoproliferative disorder (PTLD), reduction of immunosuppression to restore immune responses to EBV has response rates as high as 75% in single-center studies.10 Chronic inflammation likewise is thought to be lymphomagenic; the association between mucosa-associated lymphoid tissue (MALT) lymphoma and Helicobacter pylori gastroduodenitis is perhaps the best-known example.11

Spontaneous Regression in Hodgkin Lymphoma

Spontaneous regression of HL, as noted by the authors, has been described only rarely.12-17 A recent report of recurrent nodular sclerosing HL in a patient with Crohn’s disease, which regressed upon discontinuation of TNF-inhibitor therapy,18 suggests that host immunity may be important for the prevention or control of HL. However, overstimulation of immunity may also be pathogenic, as suggested by the association between rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, and immune thrombocytopenic purpura, and a significantly increased risk of HL.19

The cell of origin in classical HL (cHL) is almost always a germinal center (GC) or post-GC B cell.20 EBV is believed to play a causal role in one-third of cases of cHL in the developed world, although specific mechanisms of oncogenesis are not entirely elucidated.21 Transcriptional reprogramming through epigenetic mechanisms, with loss of the B-cell signature, may prevent apoptosis of these cells.22 Another important pathway implicated in cHL is the constitutive activation of the NF-κB pathway through multiple mechanisms, including overexpression of CD30 by the Hodgkin and Reed-Sternberg (HRS) cell, EBV infection, and mutations in genes encoding IκB proteins.23,24 Although not an immunomodulatory agent per se, the recently approved antibody-drug conjugate brentuximab vedotin (Adcetris, Seattle Genetics)25 targets CD30-positive HRS cells, and interrupts the
pro-survival chemokine exchange between the HRS cells and the inflammatory infiltrate that is characteristic of cHL. 

Initial clinical evidence with the immunomodulatory agent lenalidomide (Revlimid, Celgene) has shown promising results in relapsed refractory cHL. This report supports further investigation of immune dysfunction in Hodgkin lymphomagenesis and raises the exciting possibility of using immunomodulatory therapeutics for the treatment of cHL.

Acknowledgment
Samir Parekh, MD, has received funds from the Chemotherapy Foundation, a Leukemia and Lymphoma Society Translational Research Project Grant, and the Paul Calabresi Career Development Award K12-CA132783-01.

References