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.[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.

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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 × 10^3/uL, a hemoglobin of 11.8 g/dL, a hematocrit of 33.9%, and a platelet count of 99 × 10^3/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 (Figure 2). The patient was therefore diagnosed with cHL of mixed cellularity type (stage IV b), and a plan for treatment was initiated.

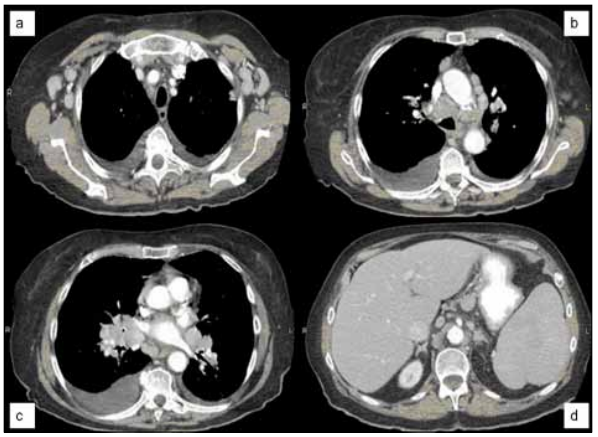

Figure 1. Initial axial contrast-enhanced computed tomography images demonstrating (a) axillary, (b) mediastinal, and (c) hilar lymphadenopathy, as well as (d) splenomegaly.

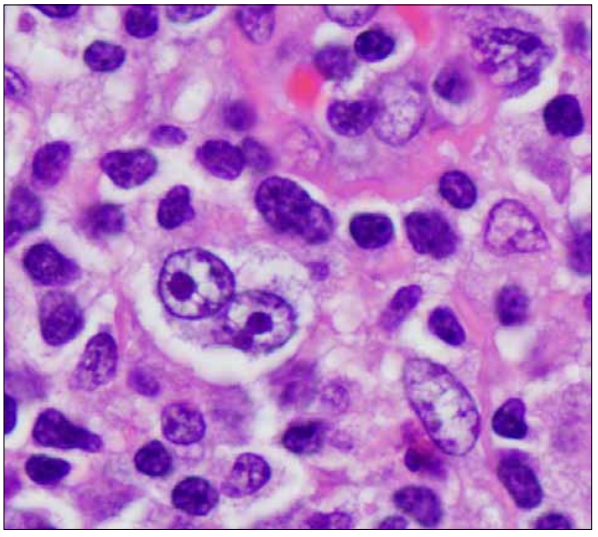

Figure 2. These large atypical lymphoid cells are morphologically consistent with classical Reed-Sternberg cells/Hodgkin cells. Hematoxylin and eosin stain, original magnification × 100.

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.

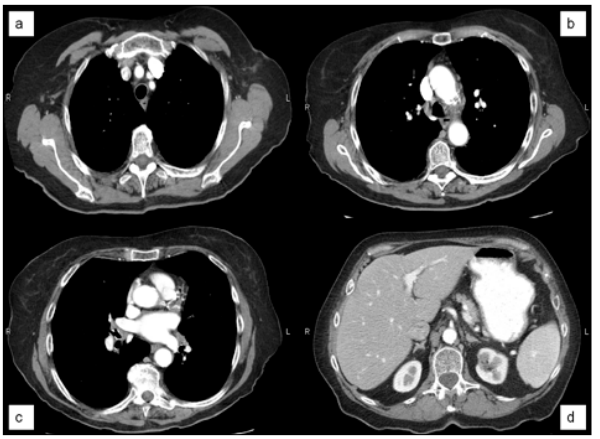

Figure 3. Subsequent axial contrast-enhanced computed tomography images demonstrating interval resolution of (a) axillary, (b) mediastinal, and (c) hilar lymphadenopathy, as well as resolution of (d) splenomegaly.

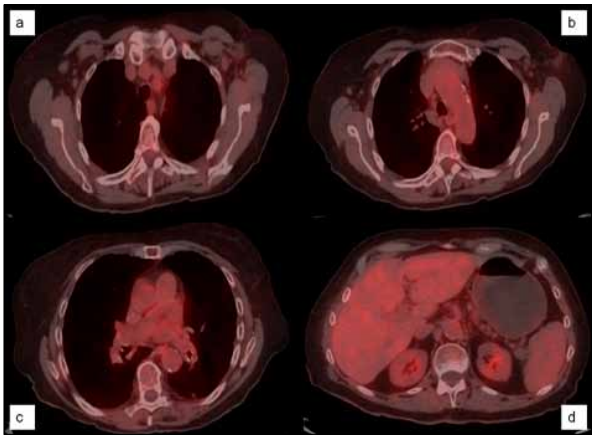

Figure 4. Corresponding axial positron-emission tomography/computed tomography images demonstrating interval resolution of (a) axillary, (b) mediastinal, and (c) hilar lymphadenopathy, as well as resolution of (d) splenomegaly, with no areas of increased hypermetabolism.

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%.[4,9,10] 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.[11-15] 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.[8,16]

The phenomenon is most often attributed to immunologic mechanisms.[17,18] 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

1. Ries LAG, Kosary CL, Hankey BF, Miller BA, Harras A, Edwards BK, eds. *SEER Cancer Statistics Review, 1973-1994, National Cancer Institute*. NIH Pub. No. 97-2789. Bethesda, MD: National Cancer Institute; 1997.
2. Horner MJ, Ries LAG, Krapcho M, et al, eds. *SEER Cancer Statistics Review, 1975-2006, National Cancer Institute*. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2006/. Based on November 2008 SEER data submission. Posted to the SEER web site, 2009. Accessed October 22, 2012.
3. Kaplan HS. *Hodgkin's Disease*. 2nd ed. Cambridge, MA: Harvard University Press; 1980.
4. Weinshel EL, Peterson BA. Hodgkin's disease. *CA Cancer J Clin*. 1993;43:327-346.
5. Stark GL, Wood KM, Jack F, et al. Hodgkin's disease in the elderly: a population-based study. *Br J Haematol*. 2002;119:432-440.
6. Weekes CD, Vose JM, Lynch JC, et al. Hodgkin's disease in the elderly: improved treatment outcome with a doxorubicin-containing regimen. *J Clin Oncol*. 2002;20:1087-1093.
7. Roy P, Vaughan Hudson G, Vaughan Hudson B, Esteve J, Swerdlow AJ. Long-term survival in Hodgkin's disease patients. A comparison of relative survival in patients in trials and those recorded in population-based cancer registries. *Eur J Cancer*. 2000;36:384-389.
8. Papac RJ. Spontaneous regression of cancer. *Cancer Treat Rev*. 1996;22:395-423.
9. Challis GB, Stam HJ. The spontaneous regression of cancer. A review of cases from 1900 to 1987. *Acta Oncology*. 1990;29:545-550.
10. Chodorowski Z, Anand JS, Wiśniewski M, Madaliński M, Wierzba K, Wiśniewski J. Spontaneous regression of cancer—review of cases from 1988 to 2006. *Przegl Lek*. 2007;64:380-382.
11. Taqi AM, Abdurrahman MB, Yakubu AM, Fleming AF. Regression of Hodgkin's disease after measles. *Lancet*. 1981;1:1112.
12. Zygiert Z. Hodgkin's disease: remissions after measles. *Lancet*. 1971;1:593.
13. Mangel J, Barth D, Berinstein NL, Imrie KR. Spontaneous regression of Hodgkin's disease: two case reports and a review of the literature. *Hematology*. 2003;8:191-196.
14. Parekh S, Koduri PR. Spontaneous regression of HIV-associated Hodgkin's disease. *Am J Hematol*. 2003;72:153-154.
15. Williams MV. Spontaneous regression of cutaneous Hodgkin's disease. *Br Med J*. 1980;280:903.
16. Ono K, Kikuchi M, Funai N, Matsuzaki M, Shimamoto Y. Natural killing activity in patients with spontaneous regression of malignant lymphoma. *J Clin Immunol*. 1996;16:334-339.
17. Horn L, Horn cHL. An immunological approach to the therapy of cancer? *Lancet*. 1971;2:466-469.
18. Balkwill FR, Naylor MS, Malik S. Tumour necrosis factor as an anticancer agent. *Eur J Cancer*. 1990;26:641-644.

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[7] 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

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pro-survival chemokine exchange between the HRS cells and the inflammatory infiltrate that is characteristic of cHL.[26] Initial clinical evidence with the immunomodulatory agent lenalidomide (Revlimid, Celgene) has shown promising results in relapsed refractory cHL.[27] 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.

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References

1. Mohsen A, Ghanem H, El-Bayoumi J, Tabbara I. Spontaneous regression of classical Hodgkin lymphoma: a case report and review of the literature. *Clin Adv Hematol Oncol*. 2012:762-764.
2. Papac RJ. Spontaneous regression of cancer: possible mechanisms. *In Vivo*. 1998;12:571-578.
3. Drobyski WR, Qazi R. Spontaneous regression in non-Hodgkin's lymphoma: clinical and pathogenetic considerations. *Am J Hematol*. 1989;31:138-141.
4. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *N Engl J Med*. 1984;311:1471-1475.
5. Osler W. An Address ON THE MEDICAL ASPECTS OF CARCINOMA OF THE BREAST. *Br Med J*. 1906;1:1-4.
6. Boyd W. The spontaneous regression of cancer. Proc Can Cancer Conf. 1957;2: 354-360.
7. Cole WH. Spontaneous regression of cancer: the metabolic triumph of the host? *Ann N Y Acad Sci*. 1974;230:111-141.
8. Hislop AD, Taylor GS, Sauce D, Rickinson AB. Cellular responses to viral infection in humans: lessons from Epstein-Barr virus. *Annu Rev Immunol*. 2007;25:587-617.
9. Shimoyama Y, Yamamoto K, Asano N, Oyama T, Kinoshita T, Nakamura S. Age-related Epstein-Barr virus-associated B-cell lymphoproliferative disorders: special references to lymphomas surrounding this newly recognized clinicopathologic disease. *Cancer Sci*. 2008;99:1085-1091.
10. Tsai DE, Hardy CL, Tomaszewski JE, et al. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. *Transplantation*. 2001;71:1076-1088.
11. Sagaert X, Van Cutsem E, De Hertogh G, Geboes K, Tousseyn T. Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development. *Nat Rev Gastroenterol Hepatol*. 2010;7:336-346.
12. Parekh S, Koduri PR. Spontaneous regression of HIV-associated Hodgkin's disease. *Am J Hematol*. 2003;72:153-154.
13. Bang SM, Cheong JW, Yang WI, Hahn JS. An unusual case of spontaneous remission of Hodgkin's disease after a single cycle of COPP-ABV chemotherapy followed by infectious complications. *Yonsei Med J*. 2005;46:425-430.
14. Svensson AM, Jacobson ER, Ospina D, Tindle BH. Reversible Epstein-Barr virus-negative lymphadenopathy and bone marrow involved by Hodgkin's lymphoma in a rheumatoid arthritis patient undergoing long-term treatment with low-dose methotrexate: a case report and review of the literature. *Int J Hematol*. 2006;83:47-50.
15. Mangel J, Barth D, Berinstein NL, Imrie KR. Spontaneous regression of Hodgkin's disease: two case reports and a review of the literature. *Hematology*. 2003;8:191-196.
16. Taqi AM, Abdurrahman MB, Yakubu AM, Fleming AF. Regression of Hodgkin's disease after measles. *Lancet*. 1981;1:1112.
17. Zygiert Z. Hodgkin's disease: remissions after measles. *Lancet*. 1971;1:593.
18. Cassaday RD, Malik JT, Chang JE. Regression of Hodgkin lymphoma after discontinuation of a tumor necrosis factor inhibitor for Crohn's disease: a case report and review of the literature. *Clin Lymphoma Myeloma Leuk*. 2011;11:289-292.
19. Kristinsson SY, Landgren O, Sjöberg J, Turesson I, Björkholm M, Goldin LR. Autoimmunity and risk for Hodgkin's lymphoma by subtype. *Haematologica*. 2009;94:1468-1469.
20. Farrell K, Jarrett RF. The molecular pathogenesis of Hodgkin lymphoma. *Histopathology*. 2011;58:15-25.
21. Roman E, Smith AG. Epidemiology of lymphomas. *Histopathology*. 2011;58:4-14. doi: 10.1111/j.1365-2559.2010.03696.x.
22. Ushmorov A, Leithäuser F, Sakk O, et al. Epigenetic processes play a major role in B-cell-specific gene silencing in classical Hodgkin lymphoma. *Blood*. 2006;107:2493-2500.
23. Horie R, Watanabe T, Morishita Y, et al. Ligand-independent signaling by overexpressed CD30 drives NF-kappaB activation in Hodgkin-Reed-Sternberg cells. *Oncogene*. 2002;21:2493-5203.
24. Emmerich F, Meiser M, Hummel M, et al. Overexpression of I kappa B alpha without inhibition of NF-kappaB activity and mutations in the I kappa B alpha gene in Reed-Sternberg cells. *Blood*. 1999;94:3129-3134.
25. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med*. 2010;363:1812-1821.
26. van den Berg A, Visser L, Poppema S. High expression of the CC chemokine TARC in Reed-Sternberg cells. A possible explanation for the characteristic T-cell infiltrate in Hodgkin's lymphoma. *Am J Pathol*. 1999;154:1685-1691.
27. Leong JW, Fehniger TA. Human NK cells: SET to kill. *Blood*. 2011;117:2297-2298.

Erratum

Due to an editorial error, pomalidomide was paired with an incorrect trade name and pharmaceutical company in the following article: Sher T, Hayman SR, Gertz MA. Treatment of primary systemic amyloidosis (AL): role of intensive and standard therapy. *Clin Adv Hematol Oncol.* 2012;10:644-651. Pomalidomide does not yet have a trade name, and the correct pharmaceutical company is Celgene. The publisher regrets the error.