



## Pulmonary Hodgkin Lymphoma in a Patient with Crohn's Disease

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Classical Hodgkin lymphoma (HL) accounts for approximately 4.5% of all lymphomas in Korea. It is almost always a node-based lymphoma, and a primary extranodal manifestation of this disease is unusual. Interestingly, patients with a history of inflammatory bowel disease (IBD) who are treated with immunosuppressants have been noted to have an increased risk of lymphoma; most cases that have been identified in this setting involve non-Hodgkin lymphoma (NHL). There have been few reported cases of primary intestinal HL in Crohn's disease (CD) patients,<sup>1</sup> and the development of extraintestinal HL in patients with CD has been reported even less frequently.<sup>2,3</sup> Herein, we describe a case of CD and small bowel obstruction complicated by the development of pulmonary HL in a 27-year-old man.

### CASE REPORT

A 27-year-old male was admitted to the emergency room with nausea, vomiting and diffuse abdominal pain. He had a long-standing history of CD (since 2009) and was being treated with prednisone (50 mg/day), mesalazine (1.5 g/day), and azathioprine (50 mg/day). He received adalimumab (tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ] antagonist) twice (160 mg at week 0 and 80 mg at week 2) in order to control recurrent abdominal discomfort and diarrhea. Abdominal computed tomography (CT) and X-ray revealed a small bowel obstruction and a suspicious mass-like lesion in the right lower lobe of lung. Subsequent chest CT showed a mass approximately 3 cm in diameter in the right low-

er lobe (Fig. 1) and another two nodules in the right upper lobe with multiple lymphadenopathy in the mediastinum, neck, and supraclavicular areas. We performed segmental resection of the small bowel, wedge resection of the right lower lobe of lung, and mediastinal lymph node biopsy.

The histopathologic findings of the lung showed a nodular growth pattern, separated by fibrous bands. The lymphoid nodule included scattered large atypical cells, resembling Hodgkin and Reed-Sternberg cells, in abundant reactive and inflammatory background including lymphocytes, plasma cells and histiocytes (Fig. 2B). The atypical large lymphoid cells were positive for CD30, CD15, and PAX5 (Fig. 2C, D), and negative for CD3 and CD20. These cells were negative for Epstein-Barr encoding region *in situ* hybridization. The histologic diagnosis, even conjunction with immunohistochemical stainings, was consistent with classical HL, nodular sclerosis type. Adjacent lung parenchyma was unremarkable with fibrinous exudates and foamy histiocytes in the air spaces at the edge of mass (Fig. 2A). The mediastinal lymph node was biopsied and exhibited the same histologic findings of classical HL. Segmental resection of the small bowel was histologically compatible with CD, and there was no evidence of malignancy. A tuberculosis-polymerase chain reaction study was negative.

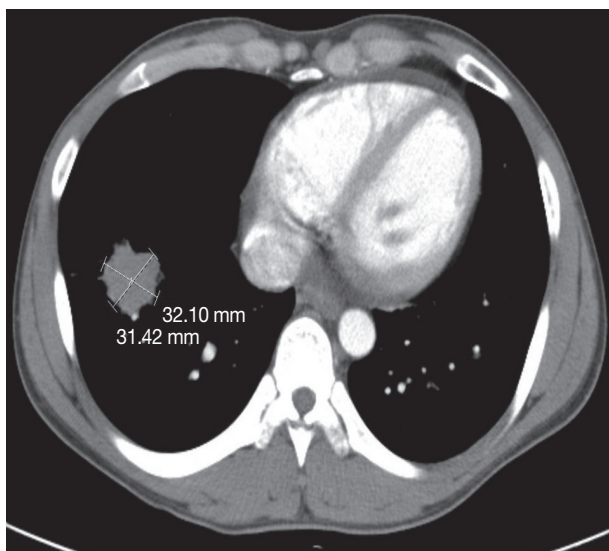
Consequently, the patient was referred to oncology. A bone marrow smear and biopsy for staging were negative. The patient was started on chemotherapy with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD). Adalimumab infusion was immediately discontinued; however, the patient continued to receive oral mesalazine to control CD. At five-month follow-up after one cycle of ABVD, the patient showed a good response, with complete resolution of the lung mass and lymphadenopathy on F-fluorodeoxyglucose-positron emission tomography/computed tomography.

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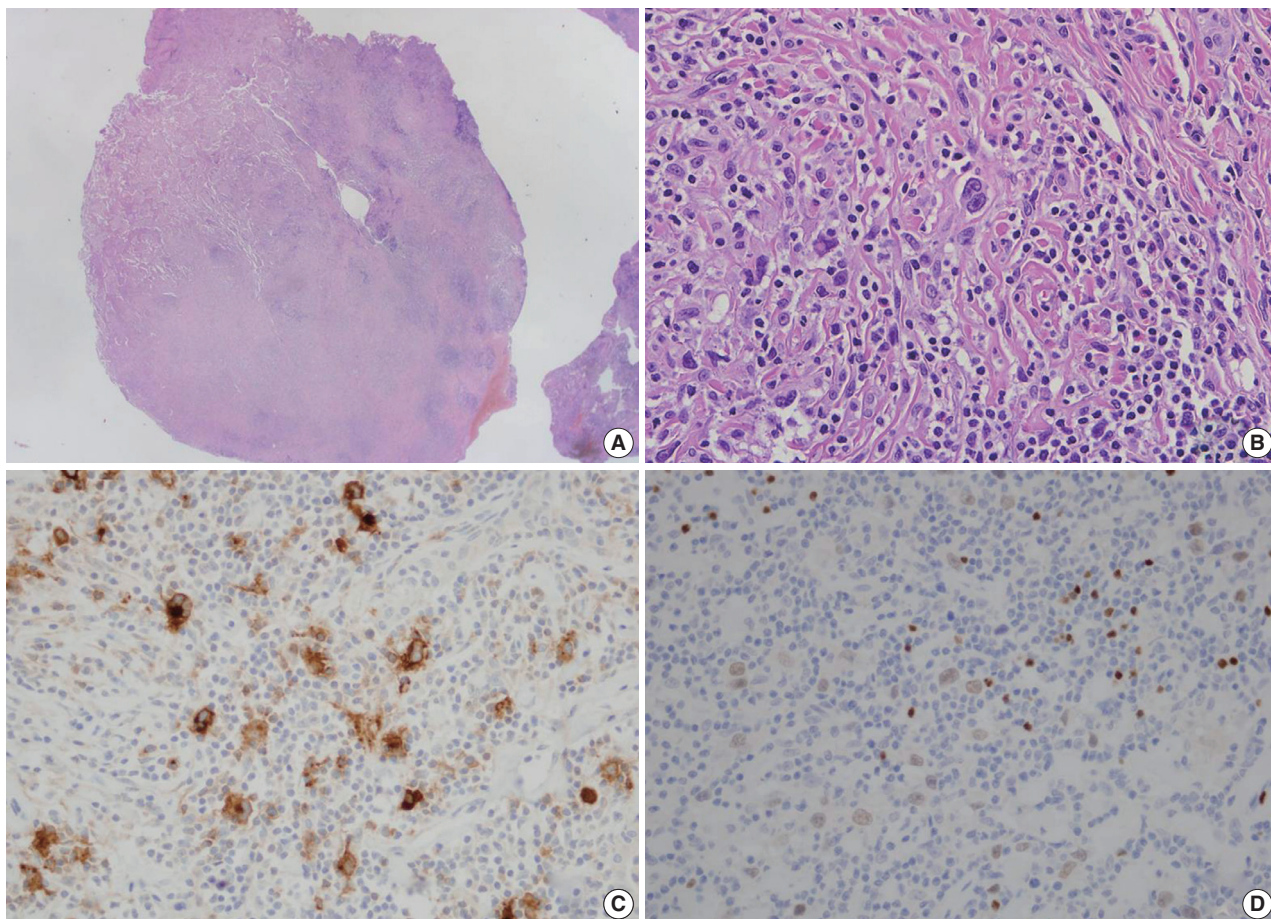


**Fig. 1.** Computed tomography scans of the right lower lobe of the lung reveal a round mass approximately 3 cm in diameter.

## DISCUSSION

IBD-affected patients treated with immunosuppressive agents such as thiopurine (azathioprine) and anti-TNF- $\alpha$  (infliximab, adalimumab, etc.) are at increased risk of malignant lymphoma.<sup>1</sup> Recently, some cases of classical HL arising in the setting of iatrogenic immunodeficiency have been reported; these diseases usually present in lymph nodes and are commonly associated with Epstein-Barr virus (EBV) infection.<sup>4</sup> The most common subtypes are diffuse large B cell lymphoma, follicular lymphoma and Hodgkin lymphoma.<sup>1</sup> Cases of primary intestinal HL in CD patients are commonly reported,<sup>5</sup> but only a few isolated cases of HL in CD patients have been described in extra-intestinal sites, such as the cervical and supraclavicular lymph nodes.<sup>2,3</sup>

The mechanism underlying the association between CD and lymphoma remains unclear. Many patients with CD receive a



**Fig. 2.** The wedge resection specimen of the lung mass shows classic signs of Hodgkin lymphoma. (A) At low power, the neoplastic mass exhibits a dense cellular area with a nodular pattern separated by fibrous bands. (B) Reed-Sternberg cells are scattered in a background of small lymphocytes. Hodgkin and Reed-Sternberg cells are positive for CD30 (C) and PAX5 (D).

combination of several immunomodulating agents, which complicates the interpretation of the role of any specific agent. Treatment with immunosuppressive agents, including TNF- $\alpha$  antagonists, changes the immunologic state of patients, and thus may lead to the development of lymphoma.<sup>6</sup> Although most reported cases are NHL, a few cases of HL have been described in patients who received TNF- $\alpha$  antagonist therapy.<sup>7</sup> The patient described in that study received two cycles of adalimumab eight weeks before he was diagnosed with HL. The interval between the initiation of therapy with TNF- $\alpha$  antagonists and the development of lymphoma, including HL, was very short (median, 8 weeks) in that study;<sup>7</sup> therefore, we suggest that in this case, the pathogenesis of HL may have involved the patient's treatment with TNF- $\alpha$  antagonist.

Azathioprine (thiopurine) has been used for therapeutic purposes to maintain remission in patients with CD. The association between azathioprine and an increased risk of lymphoma in patients with IBD was also reported.<sup>8</sup> In our case, the patient had a four-year history of CD and received azathioprine therapy with prednisone and mesalazine. The interval between his initial treatment with azathioprine and the development of HL was about four years. Farrell *et al.*<sup>8</sup> reported a patient with NHL that was detected after two years of mesalazine, prednisolone and azathioprine treatment for CD. Although, it is still controversial whether azathioprine is related to the pathogenesis of lymphoma in patients with IBD, the possibility of lymphoma should always be considered in treating CD.

Primary intestinal HL, as a consequence of underlying CD, may have a strong association with EBV. EBV-associated HL usually involves the colorectal regions.<sup>5</sup> In our case, there was no evidence of an EBV infection in surgical specimens or blood serologic evaluations. Dahhan *et al.*<sup>2</sup> reported that EBV was positive only in blood serology, and absent in both bone marrow and lymph node biopsy specimens, in primary HL in a CD patient. EBV-related lymphomas are associated with methotrexate, suggesting that defective immunosurveillance is important in lymphomagenesis. However, the development of lymphoma related to cyclophosphamide/azathioprine was EBV-negative in over 75% of cases, and had frequent p15 and p16 methylation; this could suggest that direct drug-induced mutagenesis may be involved in the pathogenesis of lymphoma.<sup>9</sup>

Therefore, our case of EBV-negative HL may be explained by other possible causes, such as molecular alteration and/or mutation.

In conclusion, many factors may influence the development of lymphoma in patients with CD, and we were not able to clearly

define the role of any specific immunomodulating drug in lymphomagenesis in this particular case. Although the patient's CD and associated treatment were of relatively short duration, the cumulative dose of azathioprine over four years and recent additional therapy of TNF- $\alpha$  antagonist may have influenced the pathogenesis of HL. Thus, in treating patients with CD using immunosuppressive therapy, it is important to closely follow patients and be aware of this potential complication.

### Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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