Hodgkin’s Disease Complicated by Cryptococcemia

— One Case Report —

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ABSTRACT

A case of Hodgkin’s disease which was complicated by disseminated cryptococcemia terminally is reported.

The patient was a 19 year old girl and complained of high fever with shaking chills and dyspnea. In the past history, antituberculous treatment was given using PAS, INH and streptomycin for 2½ months under the diagnosis of tuberculous pleurisy and several antibiotics and steroids were also given. On admission, antituberculous treatment was continued and prednisolone was also prescribed. She was discharged 15 days later but was readmitted because of abdominal pain and uncontrollable fever. On the third hospital day, a leftcervical lymphnode biopsy revealed.

Hodgkin’s disease, paragranuloma type. Endoxan and cobalt 60 irradiation were given to the abdomen. On the sixtieth hospital day, she became irritable and comatose and expired.

At autopsy, disseminated Hodgkin’s sarcoma was noted involving multiple lymphnodes, esophagus, small and large intestines, pancreas, liver, spleen, diaphragm, lungs, peritoneum, uterus, left ovary and bone marrow. In addition, evidence of cryptococcemia involving kidneys, lungs, heart, brain, pituitary gland and lymphnodes, was noted.

A brief review of the literature was also made.

Infections are frequently encountered during the course of patients with neoplastic diseases including Hodgkin’s disease. Herpes zoster, tuberculosis, and fungal diseases, especially cryptococcosis have been described as common complications.

Freeman and Weidman (1923) reported that among 165 cases of cryptococcosis, 14 cases had Hodgkin’s disease, and Casazza, et al. (1966) stated that 4 patients had cryptococcal infection as a complication among their 51 cases of Hodgkin’s disease.

The intrinsic nature of Hodgkin’s disease, adrenal corticoid therapy, and chemotherapy have been reported as factors which predispose to and account for the increased incidence of fungal diseases in these patients.

The following case represents an example of disseminated cryptococcal septicemia in a patient with rapidly progressing Hodgkin’s disease.

CASE REPORT

First admission:

The patient, a nineteen year old Korean girl, was admitted to Severence Hospital on December 15, 1969, complaining of high fever
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with shaking chill and dyspnea. She had been in good health until four months prior to this admission.

She had been admitted to two other hospitals where she was diagnosed as having tuberculous pleurisy, and antituberculous treatment had been given, using PAS, INH and streptomycin for two and a half months. Several antibiotics such as chloramphenicol, vibramycin, erythromycin, kanamycin, and prednisolone were also prescribed, but the symptoms did not subside and she was transferred to this hospital. Her past and family histories were not contributory.

On admission, temperature was 38.7°C; respiration, 24 per minute; pulse rate, 80 per minute and blood pressure, 110/70 mmHg. She was moderately well developed and nourished, but looked chronically ill. The skin, eyes, ears, nose and throat were not remarkable. A non-tender, and freely movable lymphnode is noted in the left cervical region and measured 1 x 1 cm.

On auscultation, the breath sounds were diminished in both lower lung fields but no rales or wheezing sounds were audible. The heart seemed to be located in usual site and presented regular sinus rhythm without murmur or thrill. The abdomen was soft but no palpable masses were noted. Other physical signs were not remarkable. The laboratory findings were; hemoglobin, 12.1 gm per 100 ml; hematocrit, 40 per cent; white blood cell count, 12,200 per cubic millimeter (segmented neutrophil, 79%; lymphocyte, 16% and monocyte, 5%); reticulocyte, 0.9%; platelet count, 220,000 per cubic millimeter; bleeding time, 1 minute; coagulation time, 5 minutes; erythrocyte sedimentation rate, 56 mm per hour (corrected ESR, 40 mm per hour). The urinalysis was within normal limits but the stool examination showed eggs of T. trichiurus. Chest x-ray film showed moderate degree of pleural adhesion with effusion bilaterally, but the heart, mediastinum and pulmonary parenchyma were within normal limits. Direct and concentrated sputum smears and culture for acid fast organisms were negative. Skin tests for tuberculin, paragonimus and clonorchis were all negative. Anti-tuberculous treatment was continued and prednisolone was given for 10 days, 10 mg per day under the diagnosis of tuberculous pleurisy. Body temperature fell to 36°C on the second hospital day but rose again to 38°C and continued, but on the fourteenth hospital day, the general condition of the patient was somewhat improved, the temperature returned to normal and the patient was discharged on the fifteenth hospital day. After discharge, abdominal pain and uncontrollable fever developed from January 12th, 1970. She visited the outpatient clinic and was diagnosed as having tuberculous peritonitis. A few days later she experienced watery diarrhea and was readmitted on January 30, 1970.

Second admission:

On admission, the patient looked worse than on the first admission, and poorly nourished. The temperature was 38.5°C; respiration, 25 per minute; pulse rate, 110 per minute; and the blood pressure, 130/90 mmHg. The conjunctiva was pale but no abnormal discoloration was visible from the sclera. A bean sized, hard but non-tender lymphnode was noted in cervical area on the left side, and seemed to be not enlarged, compared with that of the 1st admission. On auscultation, friction rubs and moist rales were heard over the entire left lung field, and the breath sounds were also decreased. Physical findings of the heart showed no abnormalities. The abdomen was moderately distended and
tympanitic on percussion but no palpable masses were noted. Tenderness was noted in the epigastrium and right upper quadrant of the abdomen. The bowel sounds seemed to be normal. Neurologic examination and other physical signs were not remarkable.

The laboratory findings on second admission were as follows; hemoglobin, 9.0 gm per 100 ml; hematocrit, 28 per cent; white cell count, 9350 per cubic millimeter (segmented neutrophil, 49%, stab neutrophil, 18% and lymphocyte, 33%); erythrocyte sedimentation rate, 40 mm per hour (corrected ESR, 24 mm per hour). Microscopic examination of urine showed 5 to 10 calcium oxalate crystals and 2 to 3 white and red blood cells per high power field. Stool examination revealed positive results for Endolimax nana, Entameba coli, Trichophalus trichiurus and occult blood, and Amoeba immobilization test was reported as significant. Chest film showed clear lung fields and a normal sized heart. The flat film of the abdomen showed no abnormal findings. Blood culture yielded no growth of pathogenic organisms for 48 hours. The direct and concentrated sputum smears and culture for acid fast organisms were negative.

On the third hospital day a left cervical node biopsy was done, which proved to be Hodgkin's disease, paragranuloma (Fig. 1).
Antiamoebic treatment including emetin hydrochloride, and chloroquin was started. On the sixth hospital day, the patient complained of abdominal pain and distension and became lethargic.

The bowel sounds were diminished, and the antiamoebic treatment was stopped. On the ninth hospital day, endoxan was started in a dose of 200 mg per day, for 7 days. On the eleventh hospital day, signs of paralytic ileus developed.

Small bowel series revealed delayed emptying time due to partial obstruction. The laboratory findings performed on the nineteenth hospital day were as follows; total protein, 5.0 gm per 100 ml (albumin, 2.3 gm% and globulin, 2.7 gm%); total bilirubin, 23.0 mg per 100 ml, and direct one, 13.4 mg; SGOT, 32 unit; alkaline phosphatase, 8.5 Sigma unit; serum sodium, 120 mEq/L; potassium 2.7, mEq/L; chloride, 33 mEq/L; and CO2 combining power, 28 mEq/L.

On the nineteenth hospital day, irradiation was given to the upper abdomen with Co40 using 100 rad per day for the first three days and 150 rad per day for the next 14 subsequent treatments and these were continued to the 43rd day of admission. However, her condition became progressively worse and pitting edema was noted in the lower extremities. On the sixtieth hospital day, she became irritable and comatose. In the next morning she died.

Pathologic findings:

Biopsy specimen:

The specimen (S-70-406) was one round firm lymphnode which had a grossly intact capsule and measured 1 X 0.5 X 0.5 cm. On cut section, no gross abnormality was noted. Microscopically, sections disclosed an intact capsule and follicular structures at the cortex but a single focus of histiocytic and lymphocytic proliferation was noted which compressed the uninvolved cortex into the periphery without a distinct landmark transition.

These histiocytes had abundant pale and rather eosinophilic cytoplasm and medium sized nuclei, and a few of them contained phagocytized nuclear debris. Some multinucleated cells resembling Reed-Sternberg cells were found.
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The lymphocytes were compact and appeared mature. There was no evidence of fibrosis or eosinophilic infiltration.

Autopsy findings (A-70-26):
Gross findings;

External examination disclosed a moderately icteric skin and sclera, and many enlarged, firm but movable lymphnodes were palpated in both axillae and inguinal regions. Internal examination of the thoracic cavity disclosed many enlarged and firm lymphnodes. Both pleurae showed marked adhesions. Pericardium and heart revealed no remarkable findings grossly.

Lungs were mildly edematous but no active consolidated areas were found, and weighed 520 gm and 300 gm each.

The heart and pericardial sac were not unusual. From the abdominal cavity, serous fluid flowed out and was estimated around 7500cc. The peritoneal surfaces and omentum were so adherent that the removal of the intestines was unusually difficult, but no completely obstructed focus was noted. The mesenteric lymphnodes were enlarged and firm.

The esophagus had the usual mucosa except focal erosive lesions at esophagopharyngeal junction. The stomach had rather hypertrophic mucosal pattern. No ulcerative lesions were identified. The small intestine was rather shortened but had normal mucosa. The large intestine showed no ulcerative or inflammatory foci of its mucosa.

The liver weighed 1100 gm and was somewhat enlarged. The capsule was intact and the edge was sharp, but the parenchyma showed diffuse yellowish-brown discoloration, and was rather flabby. The gall-bladder was grossly intact but the common duct was dilated due to an irregularly infiltrating mass from the retroperitoneum.

This mass was irregular in outline and markedly friable in consistency and yellowish-grey in color. It encircled the distal portion of the common bile duct and involved a part of the head of the pancreas and the second portion of the duodenum, posteriorly.

Spleen was congested, and the capsule was fibrotic. The hilar portion was adherent to the tail of the pancreas.

Urogenital tracts and both adrenals were not unusual, but the left ovary was markedly enlarged up to 5×5×4 cm and revealed the same character as the retroperitoneal mass observed in the region of the pancreas and common bile duct.

Removing the calvarium, the dura was grossly normal, and the brain weighed 1200 gm. Multiple serial sections showed no remarkable findings.

Microscopic findings;

Multiple sections of the lymphnodes from both axillae, paratracheal, hilar, mesenteric and both inguinal regions showed the same pattern.

The nodes were enveloped by collagenous capsules. Normal cortical and medullary architecture was completely lost because of massive proliferation of atypical and rather anaplastic histiocytic cells. The cells were variable in size and shape but had abundant eosinophilic cytoplasm, and large vesicular nuclei. Many of nuclei were lobulated or formed multinucleated giant cells simulating the Reed-Sternberg cells. Some nodes disclosed necrotic foci or a minimal degree of lymphocytic infiltrations and slight fibrosis.

This sarcomatous growth was also identified in many organs, namely, esophagus, small and large intestines, pancreas, liver, spleen, diaphragm, lungs, peritoneum, uterus, left
ovary and bone marrow. The periductal mass of the duodenum was also sarcomatous. Another interesting finding was appearance of many yeast-like organisms in multiple organs which reacted characteristically to Alcian blue-PAS staining and confirmed as Cryptococcus. These organisms infiltrated heavily in the glomerular capillaries, Bowman's spaces and tubules of both kidneys, in the capillaries or sinusoidal spaces of the lungs, heart, brain, pituitary gland and lymphnodes. Except for a slight lytic change of the tubular epithelial cells of the kidneys, neither inflammatory tissue reactions nor parenchymal involvement were found. The liver showed marked bile stasis. No other specific findings were noted in other organs.

COMMENT

Hodgkin's disease is a relatively rare lymphoma among Koreans, in contrast to its higher incidence in many western countries, where the Hodgkin's disease ranks first among malignant lymphomas (Gall & Mallory, 1942; Thorson & Brown, 1955; Hurst & Meger, 1961; Bjelke, 1969). Kim et al. (1967) reported that among their 218 cases of histopathologically confirmed lymphomas, only 19 cases were classified as Hodgkin's disease, and Lee et al. (1968) collected 59 cases of Hodgkin's disease among 386 cases of lymphomas. Kinnman, et al. (1969) also reported that only 28 patients were diagnosed as having Hodgkin's disease with 20,282 biopsy-specimens during nine years of experience in Korea. Reviewing the surgical pathology report-file of our department, 29,416 biopsy specimens were examined during the last 9 years and only 8 cases were Hodgkin's diseases, revealing 4.7% of total malignant lymphoma cases. In Japan, Sakai, et al., (1969) reported that among 1820 cases of lymphoma, only 370 cases were Hodgkin's diseases. So it seems that the Hodgkin's disease is relatively less common in orientals than in caucasians.

Although the etiology and pathologic nature of Hodgkin's disease remains unknown, it has long been apparent that there is some correlation between the histologic pattern of the Hodgkin's disease and the survival of the patient. An older and still widely used classification is that of Jackson and Parker (1947) namely paragranuloma, granuloma and sarcoma.

And later, Lukes et al. (1963) proposed the following terms; (a) lymphocytic and/or histiocytic, diffuse; (b) lymphocytic and/or histiocytic nodular; (c) mixed; (d) nodular sclerotic; (e) diffuse fibrotic; (f) reticular. Jackson and Parker (1947) reported that 5-year survival for paragranuloma was 55% and for sarcoma, 0%, and 20% of paragranuloma progressed to Hodgkin's sarcoma after months or years. Dawson and Harrison (1961) had collected a group of 44 cases that they called "benign Hodgkin's disease" with a 93% five-year survival and an 85% ten-year survival. In this series, about one quarter showed a transition after five or more years to the classical type of Hodgkin's disease and go on to die. Wright (1956, 1960) also reported that paragranuloma may be considered as a variant of Hodgkin's disease and that an evolution could be present. But Smetana (1969) reported that the paragranuloma should be redefined as a reactive hyperplastic lymphadenitis with imitation of some microscopic features seen in Hodgkin's granuloma, and the presumption of transformation of Hodgkin's paragranuloma into granuloma was difficult to prove, and such instances might actually represent Hodgkin's granuloma in an early stage of development or a reactive phase in a node situated distantly to a granulomatous focus. He
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also stated that the transformation from one type of Hodgkin’s disease to another, to leukemia, or sarcoma of either Hodgkin’s reticulum or fibrous variety might be more apparent than real, reflecting perhaps the local effect of irradiation or chemotherapy upon tissues affected by Hodgkin’s disease.

In our case, the biopsy specimen which was obtained on the 3rd hospital day of the second admission showed the picture of paragranuloma or lymphocytic and histiocytic type but the autopsy specimen revealed a frankly sarcomatous pattern. Considering the short time interval, the possibility of type evolution is doubtful and it seems to be rather impossible to distinguish Hodgkin’s sarcoma from paragranuloma when small numbers of malignant cells involve the node.

Infection has been recognized as a major cause of morbidity and mortality in patients with hematologic malignancies (Hesah, et al., 1965) and Hodgkin’s disease has been reported as the type of lymphoma most frequently associated with fungal diseases (Hutter and Collins, 1962). Casazza, et al. (1964, 1966) reported the frequency, type and distribution of infections occurring during the course of patients with Hodgkin’s disease, and stated that bacterial infections were associated most frequently with mortality. But among their 51 cases, there were 6 cases of disseminated and 4 cases of localized fungal infections, such as 4 of cryptococcosis, 2 of nocardiosis, one of histoplasmosis, and three cases of candidiasis. In a study reported by Zimmerman and Rappaport (1954), 18 of 60 cases of cryptococcosis occurred in patients with malignant disease of the reticuloendothelial system and stated that cryptococcosis occurring in patients with malignant lymphoma or leukemia were usually disseminated (This was evident in our case.) and proposed that lack of resistance to infection in patients was a feature of a basic disease process.

The co-existence of Hodgkin’s disease and cryptococcosis was first reported by Freeman and Weidman in 1923 and in 1950, Gendal et al., reviewing the literature, summarized 14 such cases, and stated that the association of these two uncommon diseases occurred much too frequently to be simply a matter of chance. At that time, however, several authors had offered the possibility that infection with cryptococci might occasionally produce a tissue reaction which was similar to that of Hodgkin’s disease, but in 1947 Dubin called attention to the poor immunologic response in patients with Hodgkin’s disease and in 1950, Gendal, et al. postulated that the poor resistance of patients with Hodgkin’s disease might be a main cause of infectious complication. Recently Uitmann, et al. (1966) listed several specific contributing factors including (a) deficit in antibody formation, hypogammaglobulinemia, and lymphopenia; (b) failure of cell bound antibody mechanisms; (c) leukopenia and neutropenia secondary to replacement of bone marrow, hypersplenism, and drugs or radiation toxicity; (d) glucocorticoid administration; (e) prior administration of antibiotics; (f) debility and poor nutritional state and (g) local predisposing factors, such as tumor involvement or radiotherapy.

Resistance to infection is a complex phenomenon and a single explanation would not account for the varied infectious complications of Hodgkin’s disease.

Generally speaking, antibiotics (Harris, 1950; Woods, et al., 1951), steroids (Shulman, 1950; Levy, 1955) and antimetabolite administration (Hutter, 1959; Gruhn & Sanson, 1963) have been considered as major causes of increased
fungal infections in the general population, even though the mechanisms are not clearly defined. But Casazza, et al. (1966) reported that the role of radiotherapy, chemotherapy and steroid therapy in predisposing Hodgkin's disease patients to infection was relatively minor.

The immunologic deficit of Hodgkin's disease was well documented and characterized by a depression of delayed hypersensitivity, while the antibody formation, γ-globulin level and lymphocyte count are intact in the early stage. But finally profound lymphopenia develops in the late stage even though less specific (Aisenberg, 1966), which might be a major cause of terminal infectious complications.

The portal of entry of cryptococcosis is usually the lungs but occasionally it has been shown to be the oropharyngeal or gastrointestinal tract (Lewis, et al. 1958). In this patient, there was no consolidated lesions in the lungs and technician reported Endolimax nana and amoeba in stool, which was probably a misinterpretation of cryptococci. So the possibility of gastrointestinal origin is highly suspected.

REFERENCES

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Fig. 1. Biopsy specimen of cervical lymphnode on third hospital day of second admission. Histiocytes and lymphocytes are markedly proliferated. The lymphocytes are compact and reveal a mature picture but the histiocytes are slightly atypical and have abundant cytoplasm and medium sized nuclei. H-E stain, 430×.

Fig. 2. Lymphnode of the axilla at autopsy. Massive proliferation of atypical and rather anaplastic histiocytes is evident. H-E stain, 430×.

Fig. 3. Higher magnification of Fig. 2. The cells are variable in size and shape but have large vesicular nuclei; some have lobulated nuclei, and some form multinucleated giant cells, simulating the Reed-Sternberg cells. H-E stain, 1000×.
Fig. 4. Kidney: Round and yeast-like organisms are noted in capillary lumen and Bowman’s spaces. Alcian blue-PAS stain, 430×.

Fig. 5. Same specimen as Fig. 4. Cryptococci are found in Bowman’s space, and tubules. Alcian blue-PAS stain, 430×.

Fig. 6. Lung. The organisms are found in the capillary lumens in interstitium of the parenchyma. Alcian blue-PAS stain, 430×.