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Clinical protocol

A 40-year-old man was diagnosed elsewhere to have non-Hodgkin’s lymphoma (NHL) in January 2004. He was treated with 6 cycles of CHOP regimen, following which the disease entered remission. Six months later, he developed cervical lymphadenopathy; an excision biopsy was reported as follicular lymphoma grade III at PGIMER, Chandigarh. He received salvage chemotherapy with three cycles of DHAP (Dexamethasone, Cytarabine, Cisplatin) with partial response. He was then treated with 6 cycles of MINE (Mesna, Ifosfamide, Novantrone, Etoposide) which led to remission. Autologous stem cell transplantation was planned, but he was lost to follow-up. He came back after 6 months (April 2006) with disease recurrence.

Investigations:

- Hemoglobin: 10.6 g/dL
- Total leukocyte count: 5400/µL
- Platelets: 91,000/µL
- Serum creatinine: 1.5 mg/dL

He was treated with 1st cycle of ICE (Ifosfamide, Carboplatin, Etoposide). Following this, he developed febrile neutropenia with fever and right-sided pneumonitis. He was successfully treated with broad spectrum antibiotics and granulocyte colony stimulating factor (G-CSF).

On June 6, 2006, he received the 2nd cycle of ICE and prophylactic G-CSF. He was admitted to the hospital on June 25, 2006, with high-grade, continuous fever up to 102°F of 4 days’ duration, loose stools 8-10/day for 3 days, and diffuse abdominal pain. He also complained of reddish purpuric spots on upper limb and trunk for 3 days and gum bleeding for one day. There was no past history of tuberculosis, hypertension or diabetes mellitus.

On examination, he had multiple bilateral cervical and inguinal lymph nodes, measuring 2 cm in diameter and hard in consistency. He had pallor, temperature of 102°F, blood pressure of 90/70 mmHg, respiratory rate of 17/min and pulse rate of 89/min. Examination of cardiovascular, respiratory and central nervous system was within normal limits. Abdomen was soft with mild tenderness but no rigidity; bowel sounds were present. Liver and spleen were mildly enlarged and soft.

Investigations

The Table shows the results of laboratory tests. Urine routine, microscopy and culture were within normal limits. Blood cultures were sterile. Stool routine examination showed pus cells (++) and mucus (+). Stool culture was sterile and negative on Clostridium difficile toxin assay. Peripheral blood smear for malarial parasite was negative. Chest X-ray (June 25, 2006) showed patchy hilar and parenchymal haziness; X-ray of the paranasal sinuses on the same day showed haziness in maxillary and ethmoid sinuses bilaterally, and an incidental osteoma in the right frontal region. Plain X-ray abdomen showed dilated bowel loops.

Course and management

This 40-year-old man with relapsed and refractory NHL was admitted with febrile neutropenia and gastroenteritis. He was treated with broad spectrum antibiotics (cefipime and ciprofloxacin). He also had severe anemia and thrombocytopenia, and received multiple blood and platelet transfusions in the hospital. On fourth day of hospital stay (June 29, 2006), he developed altered sensorium. Plain computed tomography of the brain showed multiple hemorrhagic lesions. He died later that day.

Treating unit’s diagnosis

NHL, in relapse, with acute gastroenteritis, intracranial bleed, sepsis and acute tubular necrosis.

Discussion

In a patient who had been treated for NHL, presenting with fever, diarrhea, hypotension and bleeding manifestation, and investigations showing anemia,
thrombocytopenia, neutropenia with pus cells in routine stool examination, the diagnosis of an infection is highly probable.\(^1\) Hence, the question of interest is the nature of the infecting agent i.e. whether bacterial, fungal or viral. Routine blood and stool culture were found to be sterile, thereby excluding common bacterial infections. He also developed oliguria with elevated serum creatinine. This rapidly-developing renal failure could be due to sepsis-induced acute tubular necrosis, anti-cancer drugs, or chemotherapy-related thrombotic thrombocytopenic purpura. The pancytopenia could have resulted from disease progression with bone marrow involvement, bone marrow suppression secondary to the use of chemotherapeutic agents, or B cell lymphoma-associated hemophagocytosis syndrome (B-LAHS) which worsens with G-CSF therapy.

The diagnostic criteria for hemophagocytic lymphohistiocytosis\(^2\) include presence of at least 5 of the following 8 clinical and laboratory parameters i.e. fever, splenomegaly, cytopenia involving 2 or more cell lines (Hb <90 g/L, neutrophil count <1 \(\times 10^9\) /L), fasting triglycerides >3 mmol/L and / or fibrinogen <1.5 g/L, ferritin level >500 ìg/L, CD25 = 2400 U/mL, decreased or absent NK-cell activity, evidence of hemophagocytosis in bone marrow, CSF or lymph nodes.

The index patient had bicytopenia (low Hb and platelet count), fever, possibly splenomegaly and worsening symptoms following G-CSF administration. Most reports of B-LAHS are from Asian patients, especially from Japan,\(^2\)-\(^4\) and most patients died. This condition is often associated with increased serum interleukin-10 levels, which is thought to be the factor responsible for hemophagocytosis.\(^5\),\(^6\)

The other dominant symptom was diarrhea. Stool culture was not contributory though stool examination showed pus cells. The patient was immunocompromized, since he was receiving chemotherapeutic and broad-spectrum third-generation antibiotics. The infection could thus be due to gram-positive bacteria, gram-negative bacteria, fungi or viruses (such as herpes or community-acquired respiratory viruses).\(^1\) Possibility of neutropenic colitis also cannot be excluded since the patient a very low TLC towards the latter part of his illness. Neutropenic colitis has been reported in patients who had been receiving cytotoxic therapy for leukemias and also lymphomas with usually fatal outcome.\(^7\),\(^8\) It is seen with TLC in the range of 500-1000 cells/dL. When the TLC ranges between 200 to 500/dL, control of the endogenous flora gets impaired, and when the TLC is <200/dL, there is an absence of inflammatory cell response.

**Final clinical diagnosis**

A known patients with NHL, in relapse, with B cell lymphoma-associated hemophagocytosis syndrome, intracranial bleed, acute infective gastroenteritis and sepsis-related acute tubular necrosis.

**Autopsy protocol**

Straw colored fluid was found in both pleural cavities (500 mL on each side) and peritoneal cavity (1 L).

**Lymph nodes:** Multiple enlarged lymph nodes, measuring 15 to 30 mm in diameter, were identified in hilar, carinal, mesenteric and retroperitoneal groups; their cut sections were fleshy with areas of congestion. Microscopic examination of sections from several lymph nodes showed diffuse effacement of the nodal architecture. The effaced areas showed cells in uniform follicular pattern present in both cortical and medullary regions, without a distinct mantle region in each follicle. Individual cells were 2-3 times the size of mature lymphoid cells, and had irregular nuclear membrane and 1-2 conspicuous nucleoli. The lymphoma cells were seen spilling into the peri-nodal soft tissue. Immunohistochemistry showed immature lymphoid cells positive for CD20 and BCL2, but negative for CD3. In some of the lymph nodes, the malignant cells were seen in microscopic areas of hyalinization, which could be explained as the result of the previous chemotherapeutic treatment that the patient had received for lymphoma. The lymph nodes in the areas of the non-lymphomatous tissue showed reactive sinus histiocytosis with evidence of hemophagocytosis (Fig. 1).

**Stomach:** It showed a nodular hemorrhagic area measuring 15 cm along the greater curvature in the mid portion of the body. On sectioning, the nodule showed transmural hemorrhages with marked increased

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Fig. 1: Photomicrograph of lymph node to show the lymphoma cells and hemophagocytosis by histiocytes (H&E, X 240)
in wall thickness (Fig. 2). There were no occluded blood vessels in the area. Sections from the affected area showed transmural hemorrhagic infarction of the stomach. No fungus was identified. The surrounding gastric mucosa showed multiple erosions with features of chronic gastritis on microscopy. The esophagus was essentially normal. **Intestine:** There was a long, nearly 20 cm-long segment of grossly discolored, nodular, boggy colon along the ascending and the transverse colons (Fig. 3). Cut section through this segment showed markedly increased wall thickness with discoloration. Rest of the colon and small intestine showed patchy mucosal congestion, no similar large lesion. Sections from the affected colonic segment showed transmural hemorrhagic necrosis with neutrophil, lymphocyte and plasma cell infiltration. The mucosa was intact though necrotic. There were multiple entrapped mucosal and submucosal air spaces (Fig. 4). The submucosa and the subserosa also showed evidence of collagenization and fat infiltration, suggesting the presence of chronic ischemia. Many dilated and congested submucosal blood vessels and some veins showed intimal proliferation and luminal narrowing. The adjoining, grossly uninvolved regions of the colon and ileum also showed submucosal collagenization, again suggesting chronic ischemia, though blood vessels had an essentially normal morphology.

**Spleen** weighed 110 g. Cut sections showed multiple, whitish miliary-sized nodules all over the parenchyma. Microscopy showed lymphoma cells in and around the central arterioles and sinus histiocytosis with evidence of hemophagocytosis.

**Liver** weighed 1520 g, and was enlarged and firm. Histology showed diffuse microvesicular fatty change, Kupffer cell prominence, and evidence of hemophagocytosis.

**Bone marrow** showed hypocellular marrow particles with increase in fat spaces. All the three lineages were identified. There was no infiltration by lymphoma cells or evidence of hemophagocytosis.

**Lungs** weighed 930 g and showed multiple nodular hemorrhagic areas in all lobes. Several sections from hemorrhagic areas were examined and showed infarction of lung parenchyma due to occlusion of pulmonary vessels by thrombi containing fungal profiles, with morphology conforming to that of zycomycosis. Surrounding non-hemorrhagic areas showed emphysematous changes and many blood vessels containing bone marrow particles.

**Kidneys** weighed 350 g. Histology showed interstitial fibrosis with chronic inflammatory cell infiltration and periglomerular fibrosis. Some tubules showed dilatation with shedding of the tubular lining epithelial cells. There were erythrocytes and protein casts. Blood vessels were within normal limits.

**Heart** was overweight (400 g) with sub-endocardial hemorrhages along the right inflow tract. Anterior wall of the left ventricle showed diffuse discol-
oration. There was concentric left ventricular wall hypertrophy. Microscopy showed evidence of cardiac muscle hypertrophy in the form of fiber size variation and anisonucleosis. In the discolored area, cardiac muscle was deeply eosinophilic with marked variation in individual fiber size, loss of nuclei and striation, interstitial edema and extravasated red blood cells.

Brain weighed 1213 g. There were sub-arachnoid hemorrhages extending to ventricles. Microscopy showed evidence of intravascular zycomycosis.

The other organs examined were within normal limits.

Final autopsy diagnosis
In a treated case of follicular lymphoma,

1. Disease relapse in lymph nodes and spleen (grade 3, Ann Arbor stage IIIS), with hemophagocytosis in lymph nodes, liver, spleen and bone marrow,
2. Pneumatosis coli with changes of chronic ischemic enterocolitis,
3. Interstitial nephritis,
4. Fresh myocardial infarction,
5. Pulmonary and brain zycomycosis with infarction, and
6. Gastric mucosal hemorrhagic infarct.

Comments
In a patient with follicular lymphoma (FL) presenting with unexplained fever and hepatosplenomegaly, relapse of lymphoma with involvement of liver and spleen would usually be the most likely diagnosis. Disease course in FL grade 3 can be aggressive. The patient had previously responded well to the chemotherapeutic agents administered. FLs are also known to respond well to anti-CD20 monoclonal antibody. Hemophagocytosis is well known in both B cell and T cell lymphomas. B-LAHS is well documented from Asian countries, mainly Japan, but less frequently from western countries. In most of the reported cases, hemophagocytosis was observed along with lymphoma cell infiltration, in organs like bone marrow and spleen. In the index patient, the lymphoma cells were identified in spleen and lymph nodes. However, hemophagocytosis was observed not only in lymph nodes and spleen with evidence of lymphoma, but also in lymph nodes with no or partial involvement, and in liver and bone marrow with no lymphoma cell infiltration. Pneumatosis coli is a rare condition with only few case reports in the English literature. There is only one reported case in NHL in the English literature.

References

Note: This case was discussed in the student clinicopathological forum of the Institute. The clinical protocol was discussed by Dr. Anil Kumar Narasiyappa, and the pathology protocol by Dr. Nidhi Sharma. The patient was admitted and followed-up under the care of Unit I in the Department of Internal Medicine. The case was compiled by Dr. Kim Vaiphei. Correspondence to: Dr Kim Vaiphei, NO 127/C, Sector 24/A, Chandigarh. Email: kvaiphei@gmail.com