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COLLAPSING GLOMERULOPATHY IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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ABSTRACT Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal hyperinflammatory syndrome due to abnormal immune process and multiorgan infiltration by phagocytic histiocytes. Renal presentation is very rare. Collapsing glomerulopathy with underlying autoimmune disease leading to HLH is documented in the present case.

KEYWORDS : *hemophagocytic lymphohistiocytosis, collapsing glomerulopathy, antinuclear antibodies.*

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life threatening hyperinflammatory syndrome caused by hypercytokinemia due to highly stimulated but ineffective immune process. Renal presentation is extremely rare. [1,2]

Case Study

A19-year-old unmarried female was admitted with fever and left wrist cellulitis for one month. She had diarrhoea and reduced urine output for three days. History of jaundice one month ago.

On investigation haemoglobin was 5.3g/dl, WBC count 2,600/cumm, platelets 62,000/cumm. BUN 18mg/dl, Creatinine 1.1mg/dl, Total protein 4.8gm/dl, Total bilirubin 4.1mg/dl, Direct bilirubin 2.3mg/dl, Alkaline phosphatase 264IU/l, LDH 4590IU/l, SGOT 56.3IU/l, SGPT 103.2IU/l, Prothrombin time 18.6 sec, activated partial thromboplastin time 35.2sec, D dimer <4000. Tests for malaria, dengue, Leptospira, Widal and triple H were negative. Direct Coombs test was positive. Anti-nuclear antibodies (ANA) test positive in 1:100 ratio. - Right lower lobe pneumonia on X-ray chest. Ultrasonography (USG) revealed hepatosplenomegaly.

The differential diagnoses included acute leukemia, sepsis, and hemolytic uremic syndrome. She was treated with antibiotics and steroids. However, the patient expired on day three after admission.

On autopsy, kidneys were enlarged and weighed 140 gm each. The right kidney showed three lesions of 2x2 cm each, yellowish with hyperaemic borders **(Figure 1a).** Liver had nutmeg appearance of chronic passive congestion. Splenomegaly of 400gm with enlarged mediastinal and periportal lymph nodes (LN) seen. Left lung showed patchy confluent consolidation.

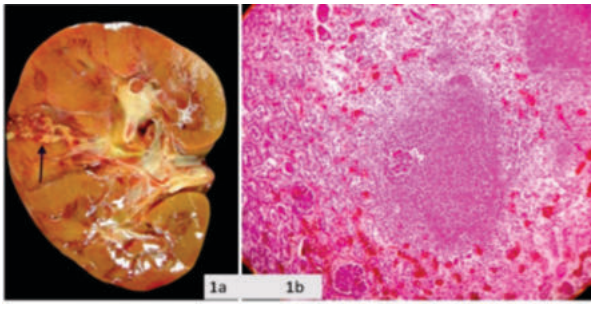

Figure 1a: Gross image of renal abscess (arrow).
1b: Microphotograph of renal abscess (H&E stain, 100x)

Histopathological examination revealed hypocellular bone marrow with histiocytic clusters showing cytoplasmic hemophagocytosis. Lymph node sinus histiocytes and splenic red pulp also showed hemophagocytosis. Renal lesions comprised of collapsing glomerulopathy, clusters of hemophagocytic histiocytes spilling into interstitium and extensive tubular necrosis **(Figure 1b, 2a, 2b).** Liver had diffuse hepatocytic microvesicular steatosis. Lungs revealed confluent bronchopneumonia.

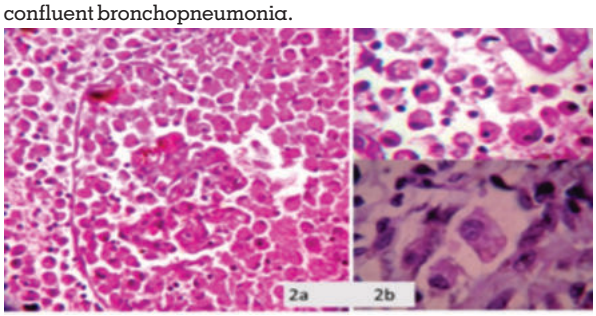

Figure 2a: Microphotograph shows collapsed glomerular tuft and histiocytic proliferation in Bowman's space (H&E, 400 x)
2b: Histiocytes with cytoplasmic hemophagocytosis (H&E, 1000X).

DISCUSSION:

Criteria for HLH include fever > 38.5°C for > 7 days, splenomegaly ≥ 3 cm along with two of the following hemoglobin < 9 g/dL, thrombocytopenia, neutropenia, and one of the following: hypertriglyceridemia (>2 mmol/L), hypofibrinogemia (<150 mg/dl), hyperferritinemia (>500 microgm/L), elevated soluble CD 25 (>2400 U/ml) and haemophagocytocis in bone marrow, spleen and lymph nodes without evidence of marrow hyperplasia or malignancy. [1,3]

Primary causes of HLH include familial and immuno deficiency, while secondary causes include autoimmune disease, malignancy, and infections by virus (EBV, CMV), bacteria (typhoid), protozoa (malaria, toxoplasma) and fungi (histoplasma, candida). Proliferation of CD8 T cells leads to excess gamma interferon production and macrophage activation. The subsequent hypercytokinemia causes tissue damage via interleukins and tumor necrosis factor (TNF). [1,4]

Treatment options include etoposide, dexamethasone, and cyclosporine. Severe, reactivated, resistant HLH warrants hemopoietic stem cell transplant. [1,5]

Our cases had high ANA levels in a female patient, suggestive of autoimmune disease with secondary HLH. Pancytopenia, splenomegaly, and LN enlargement were due to histiocytic organ infiltration. Hepatic steatosis caused deranged hepatic functions and coagulopathy. Neutropenia led to cellulitis followed by bronchopneumonia.

Renal lesions in HLH manifest in various forms such as acute tubular necrosis with collapsing glomerulopathy, minimal change glomerulopathy, and thrombotic microangiopathy. Shrinkage of glomerular tuft with vacuolation in hyperplastic podocytes is characteristic of collapsing glomerulopathy. Acute tubulo-interstitial nephritis with infiltration by CD3 T

cells and direct toxicity of IL6 & TNF α on renal tubular epithelia or podocytes are postulated to cause renal injury. [1,2]

Higher mortality in HLH is associated with increasing age, increased ferritin, and beta 2 microglobulin levels, pancytopenia, multiorgan failure and disseminated intravascular coagulation. [1,2,3]

CONCLUSIONS

HLH needs early diagnosis for adequate and targeted therapy. Renal involvement in HLH is rarely documented. Clinicians and pathologists should be alert and aware to detect this manifestation.

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