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Colonic Adenocarcinoma Presenting as Hemophagocytic Syndrome: A Case Report

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Abstract
Hemophagocytic syndrome is a rare and potentially fatal disorder characterised by pathological immune activation associated with primary familial disorder, genetic mutation or occurring as a sporadic condition. The later can be secondary to infections, malignancies or autoimmune diseases. Malignancy associated HLH is commonly seen in haematological malignancies and rarely with solid organ tumours.
We report a case of "Adenocarcinoma of colon" presenting as Hemophagocytic syndrome, to our knowledge, this is the first case report of HLH secondary to Carcinoma colon, a rare presentation of solid organ malignancy.
Keywords: *Hemophagocytosis, Carcinoma colon, Malignancy.*

Introduction

Hemophagocytic syndrome is a systemic hyperinflmmatotry disease induced by pathologic immune activation, with proliferation of well differentiated macrophages /histiocytes and increased phagocytosis of the affected organs. The syndrome was first described in 1939 by scot and Rob and again in 1952 by Farquhar and Claireaux[2]. In recent years, HLH has attracted growing attention due to an apparent inexplicable rise in its occurrence. The incidence of HLH in paediatrics is estimated as 1-225/300000 per live births and has wide geographic variations [2]. Paediatric HLH typically presents in the first year of life with unremitting fever, hepato-renal and bone marrow dysfunction with or without a positive family history. It is a recessive condition caused by mutations in genes important for NK and T-cell cytotoxic function. Homozygous null mutations in several genes have been implicated in primary HLH that causes familial HLH, FHL2-FHL5, these include PRF1, UNC13D, STX11, STXBP2 respectively[3]. Patients with congenital immune deficiency syndrome can also develop HLH due to mutations in gene that regulate immune function, example include Chediak-highashi syndrome, Hermansky pudlak syndrome etc[4]. HLH in adults is a heterogeneous entity occurring in the setting of various infectious, malignant, rheumatologic or metabolic conditions with varied clinical manifestations. Due to rarity of disease, much of our current understanding of pathology and management of HLH has been derived from research in paediatric population

with primary HLH. This article presents a case of "Adenocarcinoma of colon" in an adult presenting as HLH.

Case Report

A 42 year old male resident of Jammu, a mechanic by occupation, an ex smoker (SI-20) and occasional alcoholic, with no prior co morbidities, presented with intermittent mild to moderate grade evening rise of temperature for one year with increased intensity of fever for the last 25 days prior to admission. Constitutional symptoms were present in the form of loss of appetite and significant loss of weight (10 kg over 2 months). The patient was initially evaluated in a local hospital and was found to have pancytopenia with relative lymphocytosis with ultrasound abdomen showing hepatosplenomegaly and enlarged retroperitoneal lymph nodes. Monteux test was positive (15 mm) for which the patient was started on 4 drug ATT (duration of ATT intake at admission was for 21 days) but there was no symptomatic improvement. The patient was admitted at our centre with these complaints, for further evaluation.

General physical examination was unremarkable except for the presence of severe pallor. Mild hepatosplenomegaly was present with a firm liver which was palpable 3 cm below the sub costal margin in midclavicular line and also firm spleen palpable 2 cm below the sub costal margin along the splenic axis. Rest of the systemic examinations were unremarkable.

The differential diagnosis at admission was lympho-reticular malignancy/tuberculosis/ kalaazar/brucellosis. Patient was started on treatment as per Febrile neutropenia protocol (ANC at admission: 330). Brucella, EBV, kalaazar (rk39) and enteric serology (widal) were found to be negative and peripheral smear was negative for malarial parasites. ESR and CRP were highly elevated (132mm and 96 mg/L) and serum ferritin at admission was very high (4205, with ULN being 400). Serum fibrinogen levels were normal. The patient's counts continued to fall, requiring a cumulative transfusion of 4 pints Packed red blood cells, 7 pints platelets and 4 pints Fresh frozen plasma. The provisional diagnosis was revised to HLH (secondary to lymphoma?) (5 *out of 8 criteria were met initially-fever,cytopenias, splenomegaly, elevated ferritin and bone marrow aspirate showing hemophagocytosis- and later NK cell activity was also found to be very low, satisfying the 6th criteria*) and the patient was started on dexamethasone at a dose of 10mg/m2 with septran and fluconazole as per HLH 2004 protocol. Etoposide and cyclosporine were not started as the patient was clinically stable and these drugs would have interfered with the management of unknown primary tumour. The patient became afebrile and his counts progressively rose after 2 days of treatment. USG guided lymph node biopsy done from mesenteric lymph nodes showed features suggestive of an Adenocarcinoma with no evidence of a lymphoma. CECT abdomen revealed multiple enlarged heterogeneously enhancing lymph nodes in the mesentery, peri-portal region and retro peritoneum, with areas of necrosis within. In addition, there was nodular enhancing wall thickening in the region of proximal descending colon with surrounding fat streakiness. However there was no proximal bowel dilatation. No focal liver or adrenal lesions were seen. There was mild hepatosplenomegaly and no ascites. Note was made of large redundant loop of sigmoid colon. Imaging suggested the possibility of colonic malignancy with metastatic lymphadenopathy, however latter was far more extensive and also in non-draining areas of the colon. Colonoscopy suggested a polypoidal growth in the ascending colon (based on distance from the anal verge, however that was erroneous because of large redundant loop of sigmoid colon giving false impression of length of scope inserted) through which the scope could not be negotiated (biopsy taken). Whole body PET-CT (Figure 1) scan showed metabolically active metastatic disease involving mesenteric and retroperitoneal lymph nodes with soft tissue thickening of descending colon with tracer uptake suspicious of primary. Biopsy from the colonic growth (Figure 2)

showed features suggestive of Adenocarcinoma. The final diagnosis was thus kept as HLH secondary to Adenocarcinoma colon (stage IIIc-T3N2bM0).

In view of advanced stage carcinoma of colon with florid lymph node metastasis to even non-draining sites and in the absence of any obstructive symptoms, patient was not taken up for surgery and chemotherapy with FOLFOX-6(q2wk) regimen was started, which is a combination of Folinic acid, 5-flouro-uracil and oxaliplatin given every third week. While tapering doses of dexamethasone as per HLH-protocol patient again developed, pancytopenia and dexamethasone dose was increased to initial level along with administration of first cycle of chemotherapy and blood counts again showed rising trend. The patient has so far received 2 cycles of chemotherapy with a modest improvement in cell counts.

Table-1. HLH Diagnostic Criteria:

HLH diagnosis requires a molecular diagnosis consistent with HLH or 5/8 below criteria.

1.Fever
2.Splenomegaly
3. Cytopenias affecting 2 or more lineages. a. Hb less than 9gm/dl. b. Platelets less than 100000/cu.mm. c .Neutrophils less than 1000/cu.mm
4. Hypertriglyceridemia and/or hypofibrinogenemia. a. TG >265mg/dl. b. Fibrinogen <150 mg/dl
5. Serum ferritin > 500 micrograms/l
6. Hemophagocytosis in bone marrow, spleen or lympnnodes
7.Decreased NK cell activity
8.Soluble IL-2 receptor >2400U/ml

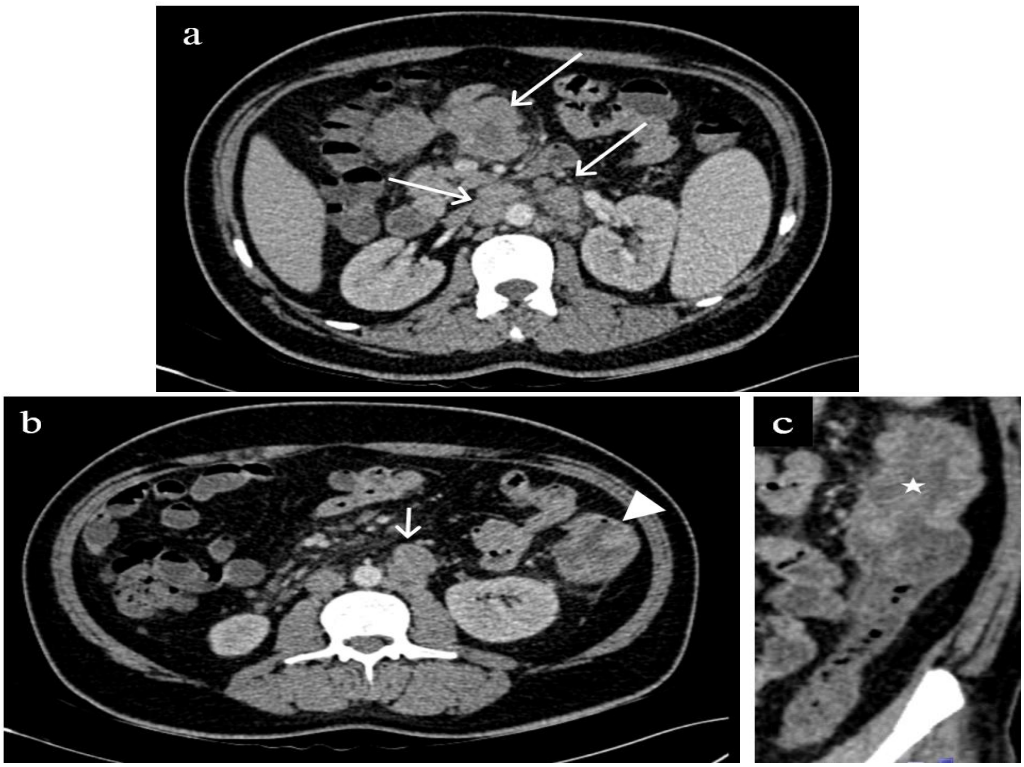

Figure 1: Axial CECT images (a and b) shows multiple enlarged heterogeneously enhancing lymph nodes in mesentery and retro peritoneum (arrows). (b) Depicts nodular wall thickening in the region of proximal descending colon (arrowhead). (c) Oblique coronal multiplanar reformat image better shows the nodular wall thickening in the proximal descending colon (asterisk). Note is made of mild pericolonic fat stranding.

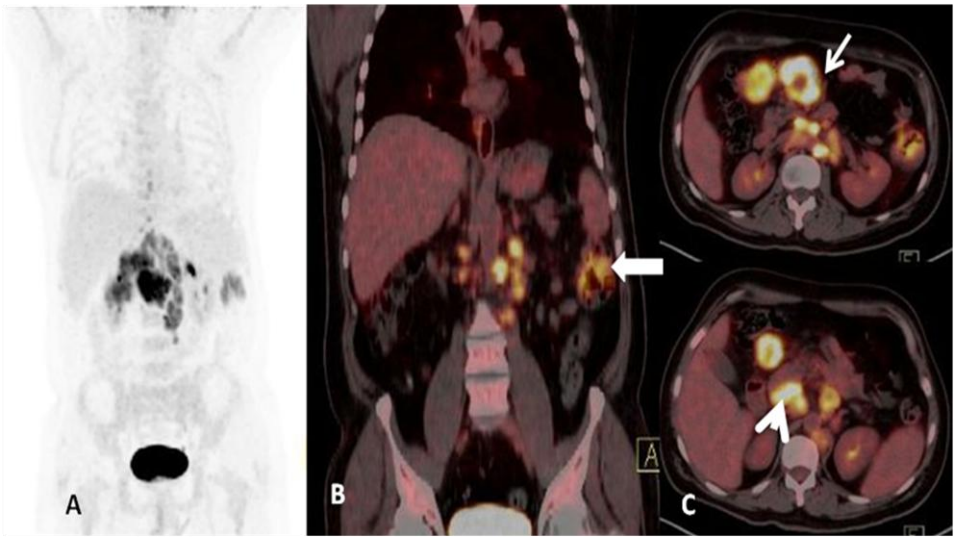

Figure 2 A: Maximum intensity projection image, B: Coronal fused PET/CT and C: Transaxial fused PET/CT images reveal abnormal tracer accumulation in the descending colon (thick arrow) and multiple enlarged nodes in the mesentery (thin arrow) and peripancreatic (arrowhead) locations showing avid FDG uptake.

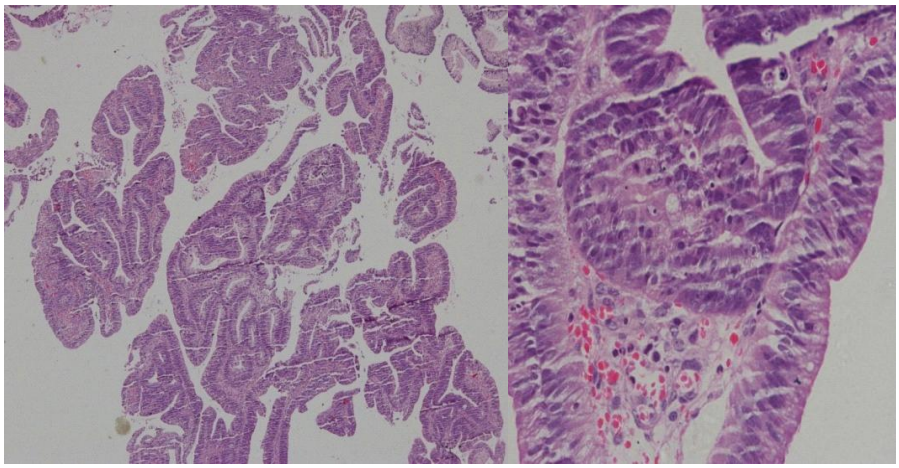

Figure 3: Colonic biopsy F/S/O Adenocarcinoma

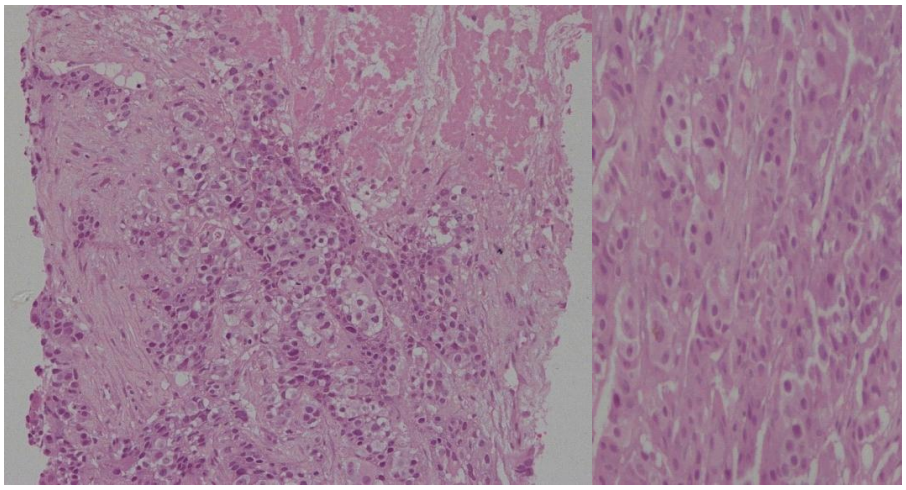

Fig-4: Mesenteric lymph node biopsy S/O Adenocarcinoma with no evidence of a lymphoma

Discussion

HLH is a rare hyper inflammatory disease, with dismal prognosis if not promptly treated[5]. Traditionally disease has been divided into Primary and Acquired. Primary HLH is caused by specific mutations in genes effecting cytolytic activity of T lymphocytes and NK- cells[6]. Secondary HLH is associated with an inciting

factor that includes infectious, malignant or rheumatologic conditions. Malignancy associated HLH is most commonly seen with lympho-reticular malignancies [7], but in recent years, HLH has been reported in association with solid organ tumours of lungs, prostate and stomach[8]. To our knowledge it is the first case of HLH associated carcinoma colon to be reported in literature. *Cristina olveria et al* reported a case of HLH in a patient operated for carcinoma colon. Postoperatively the patient developed peritonitis, HLH was attributed to that rather than the malignancy [9].

High clinical suspicion is of utmost importance for the diagnosis and early treatment. Diagnosis is suspected from clinical and laboratory criteria proposed by "Histiocyte society" and are made in the presence of at least 5 of 8 criteria[10]. (table1). Utility of these criteria is questionable because of lack of specificity. However, some author argues that despite the lack of specificity of individual criteria the ensemble that reflects the disease severity is crucial point. Fever and spleen enlargement are present in 75% of patient. Bicytopenia, hypertriglyceridemia and serum ferritin level> 500 microgram/l are present in 50 percent of cases. Literature review suggests that ferritin level > 10000 microgram/l is highly sensitive and specific and at levels >30000 micrograms/l the specificity for HLH reaches 100 percent[11].

In this case, the initial differential diagnosis was lymphoreticular pancytopenia. USG also documented mesenteric and retroperitoneal lymph nodes. Negative work-up for chronic endemic infections and investigations revealing high serum ferritin, almost up to the level specific for HLH raised the suspicion of Hemophagocytic syndrome, with bone marrow aspirate showing some evidence of hemophagocytosis. Treatment for HLH was started with report of NK cell activity awaited (later came as very low).

The frontline treatment for primary HLH is the HLH-2004 protocol. This consists of an 8 weeks "Induction therapy" with Dexamethasone, Etoposide and Cyclosporine. There are no prospective studies to guide treatment in adults with secondary HLH. Most experts suggest treatment of primary condition in mild cases. Severe cases must be treated as per HLH-2004 protocol along with the treatment of underlying condition [12]. In this case dexamethasone mono-therapy was started for two reasons. Firstly, HLH in this case was mild with no evidence of organ dysfunction except for pancytopenia, and secondly rapidly falling blood counts precluded the use of etoposide for the fear of bone marrow suppression, thus further decreasing the blood cell counts. Treatment of malignancy associated HLH is complicated and must be individualised depen-ding upon type and stage of tumour, severity of HLH and tolerability of patient for chemotherapy.

Conclusion

To conclude, HLH is a rare entity that needs a high index of clinical suspicion for diagnosis and must be suspected in any patient presenting with unremitting fever with pancytopenia. A thorough evaluation for inciting factor including solid organ tumour should be carried out in all adult patient with suspected HLH.

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