Case Report

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Internal Medicine Section

Concurrent Dengue, Tuberculosis and Secondary Haemophagocytic Lymphohistiocytosis in a Patient with Chronic Kidney Disease: A Case Report

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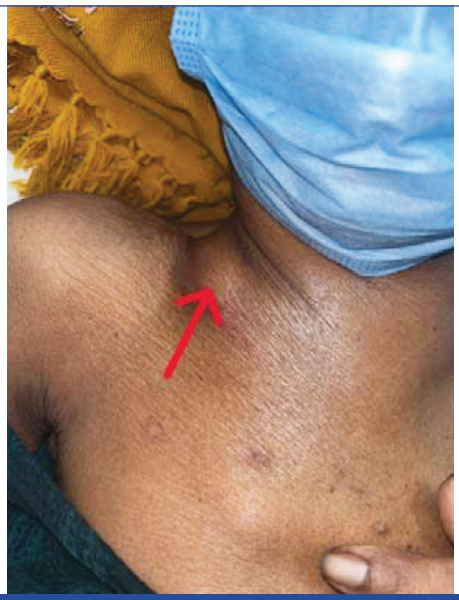
ABSTRACT

The co-existence of multiple infections in an immunocompromised patient makes it challenging to make a diagnosis, especially when there are overlapping clinical features. The present case report describes a 65-year-old female with longstanding chronic kidney disease who presented with prolonged fever, progressive breathlessness, and right supraclavicular lymphadenopathy. Three of the four co-existing conditions were definitively diagnosed: dengue infection was confirmed by positive serum Non-Structural Protein 1 (NS1) antigen and dengue Immunoglobulin M (IgM), tuberculous lymphadenitis by Fine Needle Aspiration Cytology (FNAC) and secondary Haemophagocytic Lymphohistiocytosis (HLH) using the H-score and HLH-2024 diagnostic criteria. Community-acquired pneumonia was strongly suspected based on clinical and radiological findings. Cutaneous lesions over the anterior chest wall and upper back were consistent with scrofuloderma but were not histologically confirmed. The patient received multidisciplinary care, including Anti-Tubercular Therapy (ATT), broad-spectrum antibiotics, dexamethasone and Intravenous Immunoglobulin (IVIG) (for HLH), blood product transfusions and dialysis. The literature search identified reports of concurrent dengue and HLH, tuberculosis and HLH, and dengue with tuberculosis. However, there was no published case describing the simultaneous occurrence of dengue, tuberculosis, and secondary HLH in a single patient.

Keywords: Communicable diseases, Critical care, Infections, Inflammation, Multimorbidity

CASE REPORT

A 65-year-old female presented to the emergency department with complaints of increased breathlessness (Modified Medical Research Council [mMRC] Dyspnoea Scale score of 4) for seven days, a tender right supraclavicular swelling [Table/Fig-1] and fever since one month. Past medical history was significant for chronic kidney disease (stage 5 at presentation) diagnosed 10 years earlier, for which she was on conservative medical management and had not required dialysis until presentation. There was no history of tuberculosis among her contacts or family members.



[Table/Fig-1]: Tender lymph node on the right supraclavicular area.

The fever was insidious in onset, intermittent, high-grade, and associated with chills and generalised weakness. She also complained of decreased appetite and unintentional weight loss of approximately seven kilograms over the preceding few weeks. Partial relief from paracetamol was reported.

The breathlessness was gradual in onset and progressively worsened over the last seven days. Initially occurring only on exertion, it progressed to dyspnoea during routine daily activities by the time of presentation. It was associated with productive cough with scanty whitish sputum.

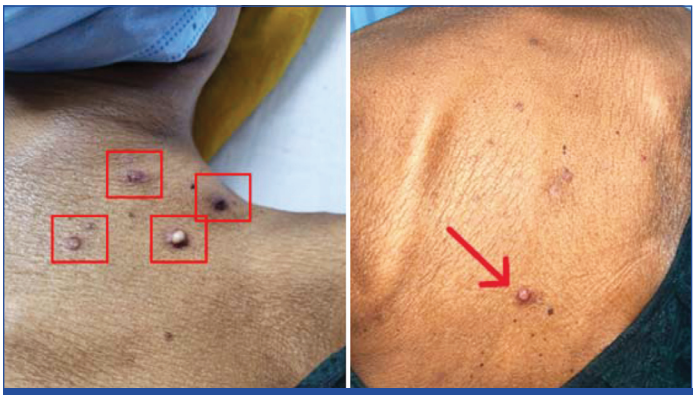
The right supraclavicular swelling had gradually increased in size over the past one month. It was associated with fever and tenderness. Intermittent discharge from the swelling was also reported, without any history of recent trauma, dental infection or similar swelling elsewhere in the body.

Three days prior to presentation, a GeneXpert assay performed on the discharge from the neck swelling at an outside facility detected rifampicin-sensitive Mycobacterium tuberculosis. She was already advised to start first-line Anti-Tubercular Therapy (ATT).

Upon initial evaluation in the emergency room, she was conscious and oriented, with a Glasgow Coma Scale (GCS) of 15/15. She appeared visibly pale and undernourished. She weighed 38 kg with a height of 144 cm (Body mass index 18.3 kg/m^2). Vital parameters at presentation revealed a pulse rate of 133 beats/min, blood pressure of 100/58 mmHg, respiratory rate of 30 breaths/min, temperature of 101°F and oxygen saturation of 86% on room air.

On general physical examination, pallor was noted. Local examination revealed a tender right supraclavicular lymph node measuring approximately 4 cm×2 cm. The swelling was tender

and firm in consistency, with reduced mobility. An overlying scar-like lesion suggestive of a healed or intermittently discharging sinus tract was present. There was no obvious fixation to deeper structures. Multiple discrete, dome-shaped papulonodular lesions measuring approximately 0.5×1 cm diameter were present over the anterior chest wall [Table/Fig-2]. Several lesions demonstrated central umbilication/pustulation, and one lesion showed evidence of central suppuration. A solitary well-defined nodular lesion with central pustulation was noted over the upper back [Table/Fig-2].



[Table/Fig-2]: Multiple discrete lesions clustered over the anterior chest wall (left). Solitary, well-defined nodular lesion with central pustulation over the upper back (right).

Respiratory system examination revealed bilateral coarse basal crepitations, with decreased air entry in the right-side. Cardiovascular and abdominal examinations were unremarkable. Neurological examination revealed no focal deficits.

Initial investigations performed in the emergency room revealed significant abnormalities [Table/Fig-3]. Following initial stabilisation, the patient was shifted to the Intensive Care Unit (ICU) for further evaluation and management.

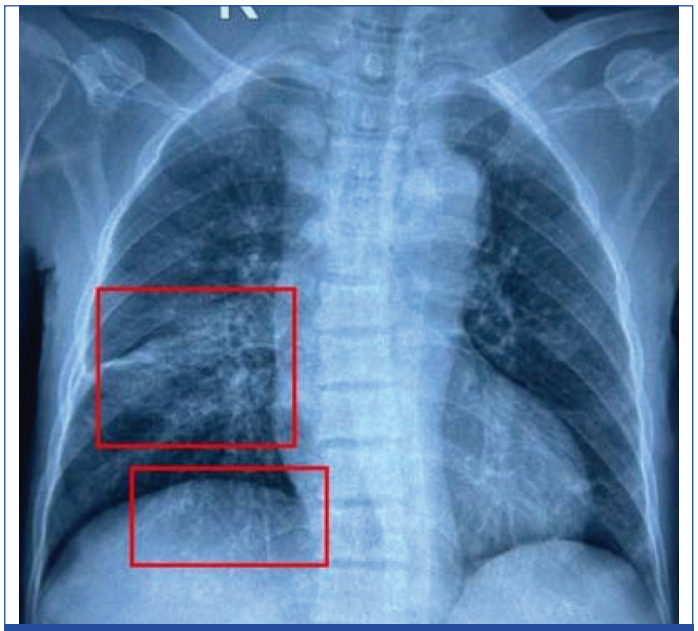
Parameters	Patient Value	Reference Range
pH	7.35	7.35-7.45
pCO_2	18.5	35-45 mmHg
pO_2	104	70-100 mmHg
K^+	4.8	3.5-5.0 mmol/L
Na^+	119	135-150 mmol/L
$Ca2^+$	0.81	0.80-1.60 mmol/L
Cl^-	93	98-108 mmol/L
Glucose	109	70-140 mg/dL
Lactate	2	0.2-2.0 mmol/L
Bicarbonate	13	18-24 mEq/L

[Table/Fig-3]: Arterial Blood Gas (ABG) analysis values. (on supplemental oxygen at 4 Lt/min).
Potential of hydrogen; pCO_2: Partial pressure of carbon dioxide; pO_2: Partial pressure of oxygen; K^+: Potassium; Na^+: Sodium; Ca^{2+}: Ionised calcium; Cl^-: Chloride.

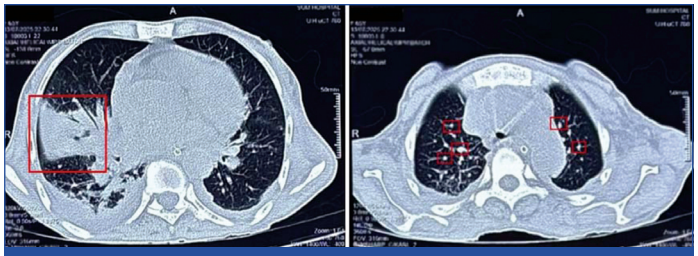
Evaluation in the ICU revealed severe pancytopenia and deranged liver function tests. Given the endemicity of tropical infections in the region, a tropical fever screening panel was performed, which returned positive for dengue NS1 antigen and dengue IgM.

Chest X-ray demonstrated patchy opacities involving the right mid and lower lung zones [Table/Fig-4]. This along with the findings of the CECT thorax [Table/Fig-5] can be correlated with the clinical findings of bilateral coarse basal crepitation with decreased air entry over the mid and lower lung zones. CECT neck demonstrated an irregular rim-enhancing lesion in the right supraclavicular region, likely representing conglomerated necrotic lymphadenopathy with abscess formation [Table/Fig-6]. Ultrasonography of the abdomen and pelvis additionally revealed chronic renal parenchymal disease, splenomegaly, and moderate ascites. FNAC of the supraclavicular lymph node was consistent with necrotising granulomatous lymphadenitis [Table/Fig-7].

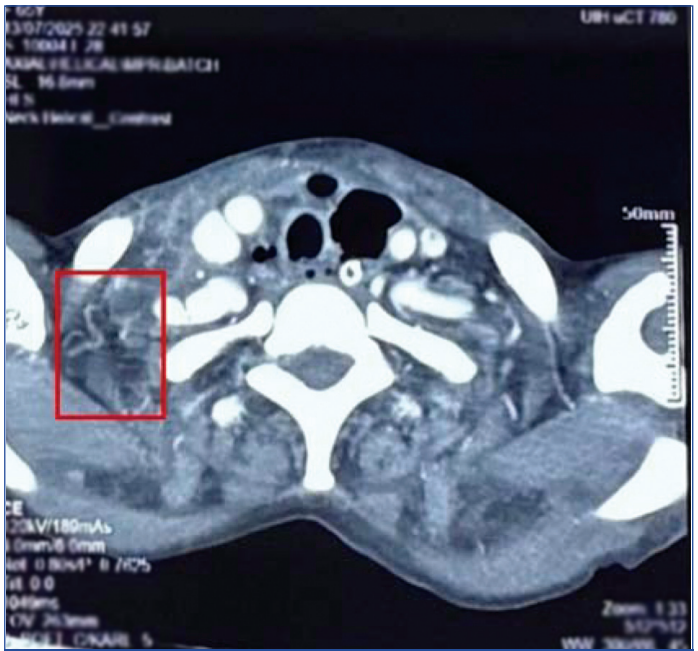
Persistent high-grade fever, splenomegaly, hepatopathy and severe pancytopenia [Table/Fig-8] prompted evaluation for secondary HLH. Since no specific validated diagnostic criteria exist for secondary HLH, diagnosis was supported by the H-score (Histiocyte Society) [1] and clinical judgement. The patient's H-score was 189, which exceeds the threshold of 169 suggestive of HLH. The HLH-2024 criteria (developed for familial HLH) were also referenced; the patient fulfilled five of the seven criteria [2].



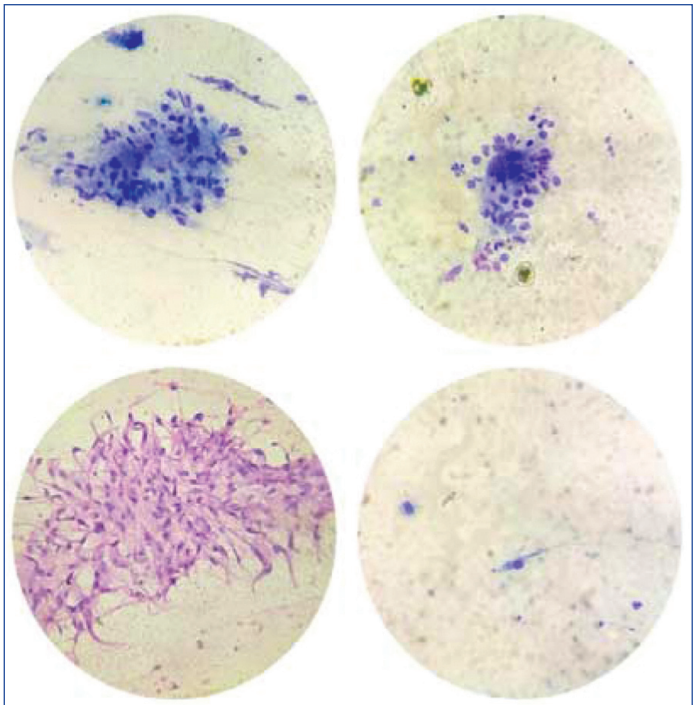
[Table/Fig-4]: Chest X-ray: Showing patchy opacities in the right mid and lower zones.



[Table/Fig-5]: Computed Tomography Contrast Enhanced (CECT) Thorax: Showing subsegmental consolidation in lateral segment of right middle lobe (left). CECT thorax: Multiple randomly scattered pulmonary nodules in bilateral lungs (right).



[Table/Fig-6]: CECT neck: Irregular peripherally enhancing lesion in right supraclavicular region likely conglomerated necrotic lymph nodes.



[Table/Fig-7]: Slides of USG-guided FNAC from right supraclavicular lymph node. From top left, clockwise: epithelioid cells, histiocytes, Fibroblast-like cells (last two).

Parameter	Patient value	Unit	Reference range
Reticulocyte count	2.95	%	0.5-2.5
Haemoglobin	5.6	gm/dL	12.0-15.0
WBC count	2.89	$\times10^3$/µL	4.0-11.0
Platelet count	7	$\times10^3$/µL	150-410
Total RBC count	2.38	$\times10^6$/µL	3.8-4.8
Packed cell volume	16.8	%	36.0-52.0
MCV	70.6	fL	83-101
MCH	23.5	pg	27-32
MCHC	33.3	g/dL	31.5-34.5
RDW-SD	61.6	fL	39-46
RDW-CV	24.2	%	11.5-14.0
Microcytic RBC	32.5	%	0.2-4.5
Macrocytic RBC	1.6	%	3.3-4.8
Serum iron	42.9	µg/dL	37-145 (adult female)
Total iron binding capacity	93	µg/dL	240-450
Serum ferritin	4306	ng/mL	13-150 (female)
Creatinine	5.45	mg/dL	0.6-1.2
Urea	135	mg/dL	6-21
Bilirubin (total)	2.5	mg/dL	0.1-1.2
Bilirubin (unconjugated)	1.97	mg/dL	0.2-0.8
AST	29	U/L	10-40
ALT	31	U/L	7-56
Alkaline phosphatase	252	IU/L	44-147
LDH	269	U/L	135-214
Fibrinogen	82	mg/dL	200-400

[Table/Fig-8]: Haematological and biochemical profile.
Abbreviations: RBC: Red blood cells; WBC: White blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; RDW-SD: Red cell distribution width- Standard deviation; RDW-CV: Red cell distribution width-Coefficient of variation; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase

Additional supportive findings included hypofibrinogenemia, elevated bilirubin, elevated Lactate Dehydrogenase (LDH) [Table/Fig-8], and underlying immunosuppression in the form of immunodeficiency secondary to CKD [3]. Definite haemophagocytosis was not seen in bone marrow biopsy.

In spite of a strong suspicion of scrofuloderma (cutaneous manifestation of disseminated TB) [4], a punch biopsy was not performed as it would not have altered the management.

A final diagnosis of disseminated tuberculosis [5] with tubercular lymphadenitis, dengue and secondary HLH was established. In addition, there was strong clinical and radiological evidence suggestive of community-acquired pneumonia [6], for which separate microbiological confirmation was not pursued.

The patient was initiated on first-line ATT (dose adjusted for Chronic Kidney Disease (CKD)) and broad-spectrum intravenous antibiotics. As a part of HLH directed therapy, high-dose dexamethasone (10 mg/m²/day, tapered per HLH-94), and IVIG (1 g/kg/day for two days) was given. Etoposide was withheld due to severe pancytopenia (absolute neutrophil count <500/µL) and critical illness to avoid further bone marrow suppression. A multidisciplinary team including internal medicine, nephrology, pulmonology, haematology, and critical care coordinated management throughout the admission. Despite the aggressive multidisciplinary management, the patient's clinical condition progressively deteriorated, with development of refractory hypotension and worsening sensorium necessitating vasopressor support and invasive mechanical ventilation. She subsequently succumbed to her illness.

DISCUSSION

As described in the case presentation, the diagnosis of dengue fever and tubercular lymphadenitis was confirmed through serology and cytology, respectively. The diagnosis of HLH was supported by an H-score of 189 and five of the seven HLH-2024 criteria. Joob B et al., described a 35-year-old man with pulmonary tuberculosis and dengue co-infection, without any mention of hyperinflammatory syndrome [7]. Similarly, Para O et al., reported a case with co-existence of dengue and HLH, without the presence of tuberculosis [8]. Therefore, to our knowledge, this is the first reported case of HLH in an adult with concurrent active tuberculosis and dengue infection.

Dengue is a well-recognised independent trigger for secondary HLH [9]. Likewise, disseminated tuberculosis leading to HLH has also been reported [10]. In the present case, the co-existence of two simultaneous infections likely acted synergistically to trigger the hyperinflammation state. Brito-Zerón P et al., examined this scenario specifically in a cohort of 151 adult patients with haemophagocytic syndrome. Infection with more than one microbiological agent was the only variable independently associated with mortality on multivariable analysis (hazard ratio 3.14, 95% CI, p=0.01), with the effect holding irrespective of the specific organism involved [11].

Management was targeted at both the infectious aetiology and HLH (dexamethasone and IVIG), along with supportive measures. Eslami A et al., in a systematic review of 213 tuberculosis-HLH patients, reported overall mortality of 39% and identified IVIG as independently associated with reduced mortality (p=0.04), age older than 44 years and comorbidities were independent risk factors for death [12]. Knaak C et al., in an analysis of 661 critically ill HLH patients with an ICU mortality of 57.8%, found a similar protective effect for IVIG, specific to the infection triggered group [13]. Etoposide was withheld given an absolute neutrophil count below 500/µL and concurrent sepsis, consistent with opinion of Naymagon L et al., that reflexive etoposide use in secondary HLH is often not appropriate and that treatment of the underlying cause is as important as treatment of the cytokine storm [14].

Several limitations deserve acknowledgement. Soluble CD25 and natural killer-cell activity assays, required for the HLH-2024 assessment, were not available locally. The initial bone marrow sample did not show definite haemophagocytosis, which is consistent with reports that the finding may be absent in early disease and that diagnosis should not rest on a single biopsy [8,12]. The normal triglyceride levels in this patient could be explained by

the fact that, hypertriglyceridemia is a late and inconsistent feature of HLH. Such variability is already reported in dengue-associated HLH [8]. Moreover, severely reduced oral intake with cachexia {Body Mass Index (BMI) 18.3 kg/m^2}, underlying chronic kidney disease and the early evolutionary stage of HLH at the time of testing are all plausible contributors to normal triglyceride value. Lastly, microbiological confirmation of community-acquired pneumonia was not pursued, as the patient was already receiving empirical broad-spectrum antibacterial therapy covering typical and atypical pathogens, consistent with American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA) guidelines [15].

Finally, the present case underlines the value of multidisciplinary care in managing critically ill patients with complex multisystem disease [16], and avoiding premature diagnostic closure [17].

CONCLUSION(S)

Concurrent active tuberculosis and dengue together precipitate secondary HLH, and the presence of two simultaneous infectious triggers carries a worse prognosis than one alone. In settings where both infections are endemic, identifying one confirmed infection in a patient with persistent fever, progressive cytopenias and rising ferritin does not exclude a second concurrent trigger. Early treatment of both infectious drivers alongside corticosteroid and immunoglobulin therapy offers the best chance of survival in this setting.

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