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A CASE OF INVASIVE FUNGAL ASPERGILLOSIS – A DIAGNOSTIC CONUNDRUM

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ABSTRACT:

In clinical practice, Pyrexia of Unknown Origin often presents a diagnostic conundrum, bridging diverse specialties such as rheumatology, endocrinology, oncology, haematology, and infectious disease. Defining PUO as per Petersdorf and Beeson, later refined by Durack and Street, involves persistent fever of 38.3°C or higher for over three weeks, eluding diagnosis despite extensive evaluations over three inpatient days or outpatient visits [1,2].

Here we present a case of invasive fungal aspergillosis in an elderly male patient, presenting with a history of persistence of fever and cough, requiring a prolonged hospitalization that posed a challenge to arrive at an appropriate diagnosis on time, despite the extensive diagnostic workup of pyrexia.

In India, PUO primarily stems from inflammatory, autoimmune and infectious etiologies, with infections comprising over 40% of cases [3]. However, current diagnostics leave over 50% of PUO cases unexplained, highlighting a significant gap in medical understanding and the need for continued research in this challenging medical phenomenon [4].

This case report emphasises on the significance of a systemic workup for PUO and the treatment dilemma despite meticulous and extensive availability of biochemical and radiological investigations.

KEYWORDS:

PUO , invasive fungal aspergillosis

CASE PRESENTATION:

A 71-year-old male patient, with a known history of Type 2 Diabetes Mellitus, Hypertension, Hypothyroidism and Ischemic Heart Disease status post Percutaneous Transluminal Coronary

Angioplasty, presented to the Outpatient Department with a one and half month history of fever and productive cough and 15 days history of headache. There was no history of weight loss, abdominal pain, chest pain, breathlessness, vomiting, loose stools, neck pain or decreased urine output.

On general physical examination, he was moderately built and nourished with BMI – 23kg/m^2. On examination, pulse rate was 100 beats per minute, regular. Blood pressure was 120/80 mmHg, SpO2 98% on room air and respiratory rate 18/min, temperature 99.6 F, pallor was present. Systemic examination were unremarkable.

Initial blood investigations showed pancytopenia with elevated Erythrocyte Sedimentation Rate. Tropical fever work up like - Dengue, Weil Felix, Leptospirosis, Brucellosis, Scrub Typhus, Widal, MPRDT, HIV, HBsAg, Anti-HCV and Paul-Bunnel tests were negative. Mantoux test was done and showed no induration. Blood, sputum and urine cultures were sent and showed no growth. RFT and ABG was within normal limits and LFT showed mild elevation of ALP and ALT. Vitamin B12, Folic Acid, and thyroid function tests were within normal limits.

Chest X ray showed no radiological abnormalities. ECG showed normal sinus rhythm. ECHO showed IHD S/P PTCA, with regional wall motion abnormality, mild MR, depressed LV systolic function; EF=45%, grade-1 LV diastolic dysfunction. USG Arterial Doppler study showed diffuse atherosclerotic disease of bilateral lower limb arteries and Venous Doppler showed no evidence of DVT. USG abdomen and pelvis showed Grade 1 fatty liver and Hepatomegaly with diffuse increase in echogenicity.

As his oxygen saturation dropped to 90 percent at room air, he was shifted to Intensive Care Unit and started on oxygen therapy around 5-6 liters per minute. He was also started on empirical IV antibiotics and other supportive medication. Despite giving empirical antibiotics, he continued to have recurrent fever spikes. Fever spikes was still persistent, so patient was started on antimalarial, antifungal (Inj. Voriconazole) and work up for recurrent fever spike was continued, while two units of PRBC were transfused in view of moderate anemia.

A bone marrow aspiration and biopsy performed revealed cellular marrow with normal erythropoiesis and later connective tissue and autoimmune workup (ANA, ANA profile, RA factor, IgG4, ACE levels) were inconclusive. Repeat chest X-Ray on day 5 of admission showed non homogenous bilateral basal opacities. Patient was started on a therapeutic trial of Antituberculosis Therapy in view of PUO.

As there was no response to ATT, further investigations such as CT scan of the thorax and abdomen showed, diffuse patchy areas of consolidation and ground glass opacities with inter-lobar septal thickening in bilateral lung fields with mediastinal lymphadenopathy and bilateral mild pleural effusion with fissural extension. X-Ray paranasal sinuses was normal.

PET-CT was performed, revealing irregular soft tissue attenuation and ground glass changes in bilateral lung (more involving superior and basal segments of bilateral lower lobes)-likely infective etiology, mediastinal and hilar lymphadenopathy-likely reactive/infective and diffuse splenic FDG uptake and diffuse marrow FDG uptake-likely physiological.

Despite treatment, the patient continued to deteriorate, developing fever spikes, tachycardia, and tachypnea, necessitating mechanical ventilation. Serial chest X-rays showed non homogenous bilateral basal opacities.

Serial monitoring of CBC, RFT and LFT were deranged. Serial monitoring of ABG showed metabolic acidosis. Serum Galactomannan assay was positive with titers of 1.22 indicating a fungal infection and then started on Injection Liposomal Amphotericin B.

Broncho-alveolar Lavage fluid analysis was positive for galactomannan. On day 22 of hospitalization, he developed hypotension and was started on inotropic agents. On day 23 of hospitalization, his condition worsened with severe hypotension requiring triple inotropic support, and deterioration in renal and metabolic parameters and unfortunately patient succumbed to his illness.

IMAGES:

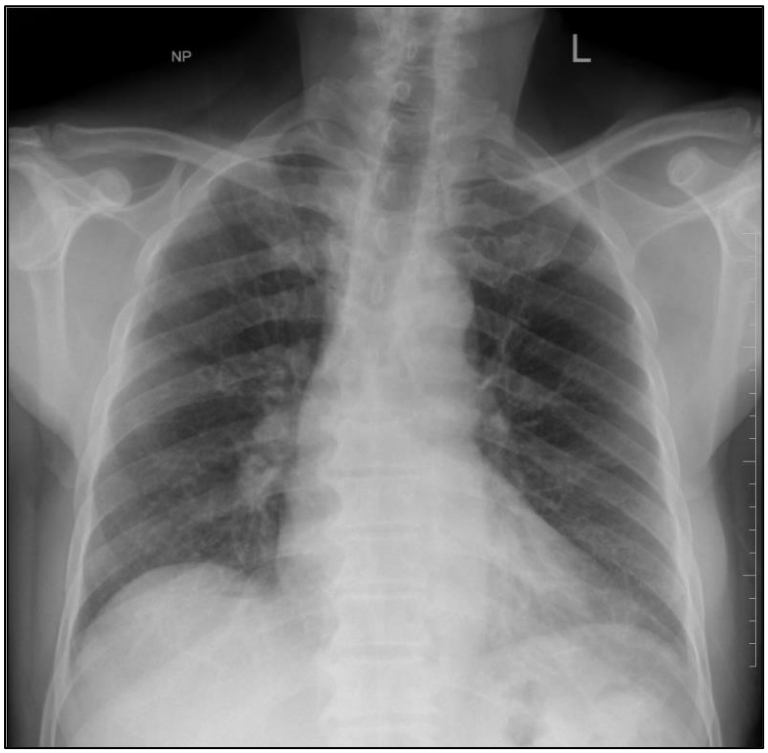

Fig 1: CXR on day 1 showing no radiological abnormalities

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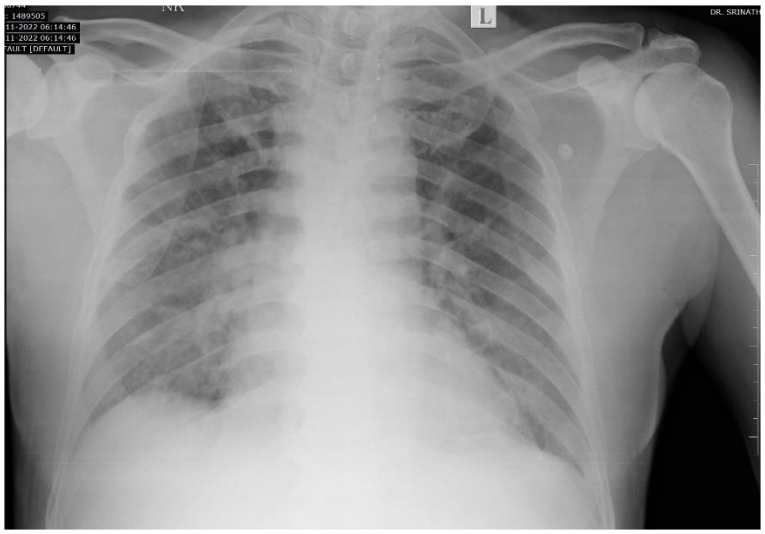

Fig 2: CXR on day 11 of admission showing inhomogenous opacities in right lower zone suggestive of consolidation

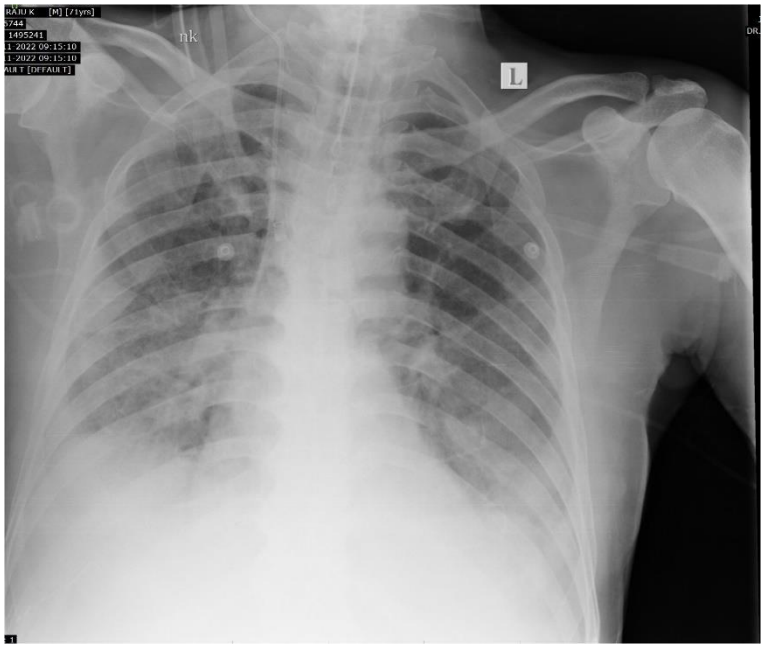

Fig 3: CXR on day 23 showing inhomogenous opacities in perihilar region in right lung field, bilateral lower zone haziness and blunting of bilateral costophrenic angles

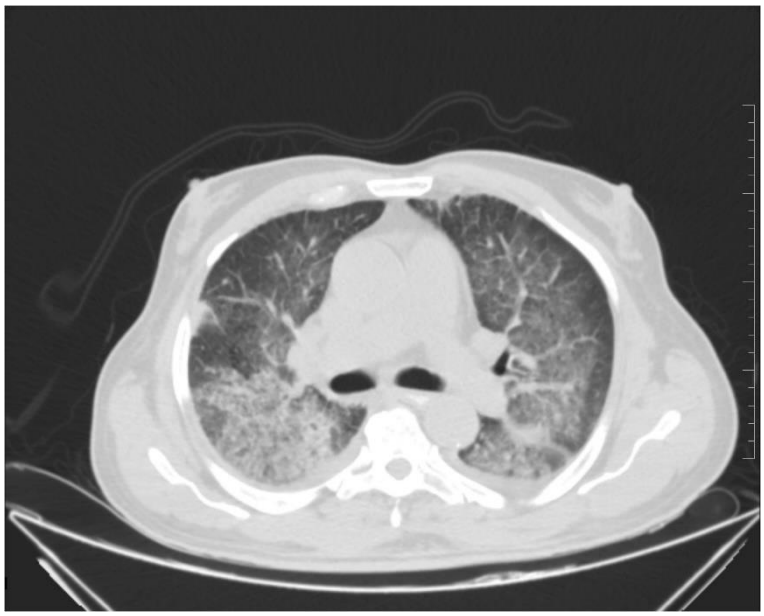

Fig 4: CT thorax showing diffuse patchy areas of consolidation and ground glass opacities with inter-lobar septal thickening in bilateral lung fields with mediastinal lymphadenopathy and bilateral mild pleural effusion with fissural extension

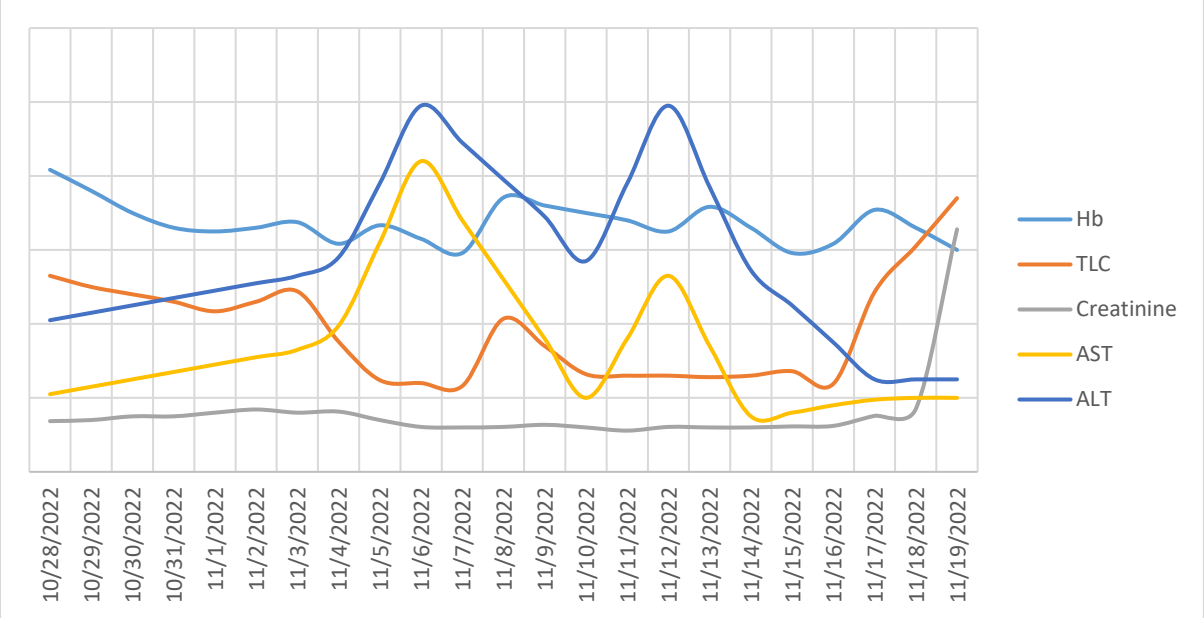

Fig 5: Summary of investigations

DISCUSSION:

Thermal regulation in our body is controlled by the preoptic and anterior hypothalamic region. Prostaglandin E2 is secreted when these areas are triggered by pathogens or inflammatory stimuli, which causes cutaneous vasoconstriction, non-shivering thermogenesis in brown adipose tissue, shivering thermogenesis in skeletal muscles and counter-regulatory cytokines like IL-10.

Endemic mycoses such as aspergillosis, mucormycosis, cryptococcosis, and histoplasmosis are opportunistic infections that predominantly affect immunocompromised individuals [5].

However, some fungal infections can also impact immunocompetent persons. Due to non-specific and overlapping clinical symptoms, such as B symptoms and either pulmonary or extra-pulmonary manifestations, early diagnosis of a fungal cause is challenging [6].

Tissue biopsies have proven to be more effective than antigen testing in detecting histoplasmosis as the causative agent [7]. Invasive aspergillosis is more commonly seen in individuals undergoing chemotherapy, on immunosuppressive medication, or long-term corticosteroid therapy. Those with pre-existing respiratory conditions like Chronic Obstructive Pulmonary Disease or bronchial asthma are particularly susceptible. Symptoms typically include fever, cough, dyspnoea, pleuritic chest discomfort, and occasionally, haemoptysis [8].

In developing countries, many invasive aspergillosis cases are either undiagnosed until it's too late for effective intervention or are only identified post-mortem [9-12]. Due to the inaccessibility of galactomannan or beta-glucan assays, direct microscopy, histopathology and culture are the primary diagnostic methods for invasive aspergillosis in most centers.

Although empirical administration of antimicrobial or anti-inflammatory drugs is common, it is crucial to first establish a diagnosis before initiating definitive treatment. Antibiotics may suppress the growth of pathogens or lead to resistance, giving a false impression of resolution. In developing countries, Amphotericin B or Itraconazole are often the first-line therapies for invasive aspergillosis, likely due to the higher cost of other effective anti-Aspergillus drugs [13,14,15].

CONCLUSION:

Despite the availability of a wide range of both non-invasive and invasive diagnostic procedures, pinpointing the cause of Pyrexia of Unknown Origin (PUO) remains a challenging task. It is often more fruitful to search for rare manifestations of common diseases rather than typical manifestations of rare diseases. A comprehensive clinical examination, detailed patient history and basic investigations remain fundamental in forming the basis for a final diagnosis

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