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Pathology Section

Images in Haematology: A Rare Visualisation of Histoplasma Capsulatum in Peripheral Blood Smear and Bone Marrow Aspirate

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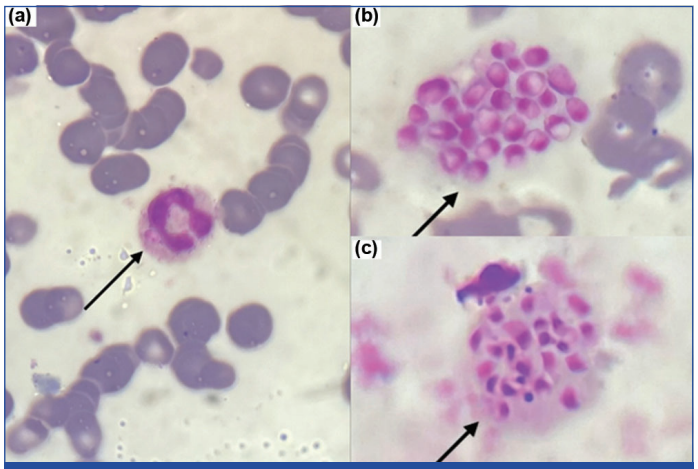
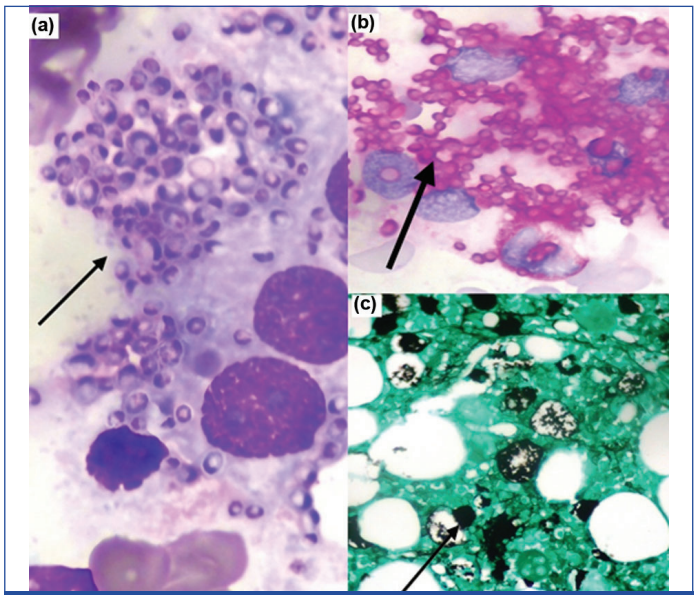
A 70-year-old Indian female with a history of Chronic Obstructive Pulmonary Disease (COPD), using an Asthalin inhaler (Salbutamol, 100 mcg/puff) (2 puffs as needed), presented with a low-grade fever, dry cough and mild hepatosplenomegaly. For fever, she was prescribed paracetamol 650 mg as needed, and for cough, benzydamine hydrochloride syrup 10 mL orally. Importantly, the patient had not received any corticosteroids. General examination revealed weight loss. On respiratory system examination, mild wheeze was noted bilaterally. Abdominal examination also demonstrated mild hepatosplenomegaly. Cardiovascular and central nervous system examinations were normal and revealed no significant abnormalities. Initial laboratory investigations showed haemoglobin 10 g/dL, total leukocyte count 7800/cu mm, platelet count 46000/cu mm, C-Reactive Protein (CRP) 36.4 mg/L, serum creatinine 1.1 mg/dL, total bilirubin 1.50 mg/dL (direct bilirubin 0.96 mg/dL), total protein 5.6 g/dL, and serum albumin 2.4 g/dL. Liver enzymes were also normal {Serum Glutamate Pyruvate Transaminase (SGPT 31 IU/L)}. The patient thus demonstrated isolated thrombocytopenia with mild anaemia and normal leukocyte count. Biochemistry showed hypoproteinaemia and hypoalbuminaemia, a slight rise in bilirubin, and increased C-Reactive Protein (CRP). Peripheral blood and buffy coat smears demonstrated intracellular and extracellular forms of Histoplasma capsulatum as shown in [Table/Fig-1]. On the peripheral smear, small (2-5 µm) oval yeast forms with narrow-based budding and a surrounding clear halo were observed, which indicated a possible capsule-like structure. The presence of intracellular organisms within neutrophils was noted, which was thus consistent with disseminated infection, whereas the extracellular clusters among erythrocytes showed uniform budding yeasts with eccentric acorn-like nuclei. Bone marrow aspirate and special stains {Periodic Acid–Schiff (PAS), Gomori Methenamine Silver (GMS)} confirmed the presence of H. capsulatum as shown in [Table/Fig-2]. The bone marrow aspirate showed small (2-5 µm) oval yeast forms with narrow-based budding, present as both intracellular and extracellular clusters, with a clear halo, which indicated the presence of a capsule. The PAS stain showed thick, magenta-stained capsules surrounding the yeasts, thus confirming the polysaccharide-rich cell wall. As a confirmation regarding the presence of fungal elements, GMS staining revealed fungal cell walls as black structures against a pale green background.

The patient was not immunosuppressed or suffering from systemic disease that was susceptible to opportunistic fungal infections. She was started on intravenous liposomal amphotericin B for two weeks in view of disseminated histoplasmosis, and oral itraconazole (200 mg twice a day). The planned duration of itraconazole therapy was 12 months, according to the guidelines of the Infectious Diseases Society of America (IDSA), which recommends long-term antifungal treatment (at least 12 months) when a patient has disseminated histoplasmosis so that the infection can be eradicated and the risk of relapse can be minimised. The patient gradually showed clinical improvement with the resolution of fever, platelet count recovery, and regression of hepatosplenomegaly at the time of follow-ups.



[Table/Fig-1]: Peripheral blood and buffy coat smears demonstrating intracellular and extracellular forms of Histoplasma capsulatum; (a) Peripheral blood smear showing intracellular yeast forms of H. capsulatum within a neutrophil as shown by black arrow (Wright-Giemsa, 1000x); (b) Peripheral smear showing extracellular clusters of small, uniform, oval yeast forms with narrow-based budding and eccentric acorn-like nuclei among erythrocytes pointed by black arrow (Wright-Giemsa, 1000x); (c) Buffy coat smear, a cluster of free budding yeast forms (Wright-Giemsa, 1000x).



[Table/Fig-2]: Bone marrow aspirate and special stains (PAS, GMS) confirming the presence of Histoplasma capsulatum; (a) Bone marrow aspirate showing extracellular clusters of yeast forms pointed with black arrow (Wright-Giemsa, 1000x); (b) PAS stain demonstrating thick, magenta-stained capsule surrounding yeast forms pointed with black arrow (PAS, 400x); (c) GMS stain highlighting fungal cell walls as black structures against a pale green background highlighted with black arrow (GMS, 400x).

Histoplasma capsulatum is a dimorphic fungus that causes histoplasmosis and is considered a disease between an

asymptomatic pulmonary infection to severe Progressive Disseminated Histoplasmosis (PDH) [1]. Although PDH has long been related to immunocompromised hosts, including Human Immunodeficiency Virus (HIV) infection and immunosuppressive therapy}, H. capsulatum can spread in immunocompetent hosts, particularly in the presence of specific risk factors [2]. Histoplasmosis has also been reported in both endemic and non-endemic areas in India; the disease has poor recognition, is frequently misdiagnosed (i.e., as tuberculosis), and is on the rise in the elderly [3]. Epidemiologic studies indicate that numerous cases of disseminated histoplasmosis in India are along the region of the Gangetic plains (West Bengal, Assam, northern India), yet it is not exclusively restricted to those regions [3]. Current literature indicates that there are risk factors, other than classical immunosuppression, which may predispose to dissemination, even in hosts who are immunocompetent [3]. These comprise the extremes of age, underlying lung pathology (e.g., emphysema, chronic lung disease) and environmental exposures (bird or bat droppings, soil-disturbing activities) and perhaps even subtle immune deficits [1,3].

Some of the differential diagnosis needs to be taken into account when small yeast-like organisms could be found in peripheral blood or bone marrow smears [4]. Leishmania donovani is the most significant mimic of H. capsulatum, as they both can have the same form of small intracellular oval bodies, but Leishmania can be distinguished by the presence of a rod-shaped kinetoplast, characteristic of Leishmania but is absent in Histoplasma [4]. Likewise, Candida glabrata can resemble Histoplasma due to its small size, but tends to be extracellular and does not have a clear halo and uniform intracellular distribution as does Histoplasma [4]. Talaromyces marneffei can also be considered as a differential diagnosis, particularly in endemic areas, although it demonstrates typical transverse septation in the yeast cells and is detected by culture or molecular techniques [4]. Other artefacts like fragments of platelets or staining debris can sometimes resemble yeast morphology, but will not be consistently fungal in morphology and will not stain with either PAS or GMS [4]. H. capsulatum, on the other hand, is generally 2-5 µm in size, exhibits intra and extracellular localisation and stains red on PAS and black on GMS histochemical stains, as observed in the present case [1,3].

In a case reported by Samaddar A et al., a 47-year-old Indian female presented with two months of high-grade and sporadic fever, generalised weakness, aches, and a non-productive cough, oral ulcers, and vomiting for the last one week [5]. She had been treated before with brucellosis and was still experiencing the symptoms [5]. Investigation showed that there were erythematous papules at the back of the neck and a white plaque at the buccal mucosa [5]. Laboratory revealed high levels of Erythrocyte Sedimentation Rate (ESR), CRP and imaging revealed mild hepatosplenomegaly and mosaic attenuation with small mediastinal lymph nodes [5]. Punch skin and mucosal lesion biopsy presented intracellular yeast-like forms of H. capsulatum, which were confirmed by PAS and GMS staining and culture with thermal dimorphism [5]. The patient received intravenous Amphotericin B, then oral itraconazole, and this treatment led to the improvement of the clinical condition with the disappearance of fever and mucocutaneous lesions [5].

In a case reported by Subramanian M et al., a 58-year-old Indian male who had no previous comorbidities reported having fatigue, weakness, syncope, and severe unintended weight loss [6]. X-rays showed bilateral enlarged adrenal glands, and a Computed Tomography (CT)-guided biopsy was positive for Histoplasma capsulatum [6]. Other results were interstitial lung disease, mediastinal adenopathy and ventriculomegaly with sizable parenchymal losses [6]. The tuberculosis, HIV and autoimmune disease workup was negative, thus a diagnosis of disseminated histoplasmosis [6]. The liposomal amphotericin B and later itraconazole were used to treat the patient [6]. He had progressive respiratory and cognitive deterioration during subsequent years, and eventually developed interstitial lung disease, COPD, and adrenal insufficiency, despite the therapy [6]. His disease was complicated by the inability to tolerate oral medications, which led to switching to comfort care, at the end of which he died [6].

The case highlights about importance of meticulous peripheral smear analysis in old-age patients having cytopenia even without presentation of classical risk factors. The diagnosis of Histoplasma in the peripheral blood of an immunocompetent host is an extremely rare case, thus emphasising the need to account for disseminated fungal infections in non-typical clinical conditions.

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