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Case Report

Fatal Multi-Organ Vasculitis with Mycosis Masquerading as Tuberculosis in an Adolescent Male

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Abstract

Introduction: Multi-organ vasculitis is known to be an inflammation affecting vessels of various calibres either in response to an immune mediated event or an infection. It is known to affect virtually all organs including the pulmonary vasculature most commonly, gastrointestinal system, urogenital system and the central nervous system.

Case Description: A 15 – year old male presented with symptoms of nasal swelling which gradually grew to involve the periorbital region along with cervical lymphadenopathy. The physical examination and laboratory investigations were within normal limits. Contrast enhanced computerised tomography revealed features suggestive of an infective etiology favouring osteomyelitis. Corticosteroids were instated to control the inflammation. However the absence of response prompted further investigation. Fine needle aspiration cytology was performed which was suggestive of an inflammatory pathology of the region. This prompted histopathological studies of the lymph node and soft tissue from the mass revealing multiple ill-formed granulomas with multinucleate giant cells and fibrosis and micro abscesses consisting of karyorrhectic debris surrounded by lymphocytes, plasma cells and histiocytes with vasculitis. Ziehl-Neelsen stain for acid-fast bacilli were negative. The final diagnosis was necrotizing granulomatous lymphadenopathy with the differentials of tuberculosis being favoured over Kikuchi's disease. Pulmonary consult indicated the institution of antituberculosis treatment. By day 19 of admission, the patient became febrile, disoriented and demonstrated aggressive behaviour. Medical and psychiatric evaluation suggested maxillary sinus osteomyelitis, with a suspicion of central nervous system (CNS) tuberculosis. Magnetic resonance imaging (MRI) revealed multifocal non-haemorrhagic infarct secondary to embolic shower, possibly secondary to tuberculosis. On day 23, he succumbed to his illness. A medical post mortem was performed following which the histopathological and microbiological studies lead to the final diagnosis of widespread vasculitis with mycosis involving the cerebrum, lungs and parotid glands.

Conclusion: The widespread occurrence of tuberculosis along with its various atypical presentation make it the most common diagnosis considered in our demographic set up. This case highlights the importance of giving equal weightage to other entities, including the spectrum of immunological illnesses such as vasculitis and other infectious agents in order to improve prognostic outcomes.

Keywords: Fatal; Multi-Organ; Vasculitis; Tuberculosis; Adolescent Male

Introduction

Vasculitides are known to involve all organ system as a pathological response to either an immune mediated inflammation or as a resultant of direct invasion by infectious pathogens [1]. Clinical manifestations may vary from granulomatosis with polyangiitis, Churg Strauss syndrome to giant cell arteritis in conjunction with many common bacterial, fungal or tubercular infections [2,3]. It is imperative to accurately identify the cause in such cases, in order to initiate appropriate therapy and contain further progression of the disease process. Herein we describe a case of multiorgan small vessel vasculitis in an adolescent male that presented as a diagnostic dilemma and culminated with fatal outcome.

Case Report

The patient, a 15-year-old, previously healthy male presented to the otorhinolaryngology outpatient department with a gradually progressing diffuse nasal swelling extending to the left periorbital region along with nasal congestion and watering from the left eye, of two months duration. This was associated with multiple episodes of spontaneous nasal bleeding aggravated by sneezing. There were no precipitating factors, or any history of past medical or surgical ailment. Family history was non-contributory.

General physical examination was within normal limits, while local examination revealed a diffuse, hard, non-tender swelling on the dorsum of nose extending upto the lower left eyelid. This was associated with deviation of the nasal septum to the right side along with congestion of the nasal mucosa. Multiple bilateral level II and level III lymph nodes were palpated, largest being 1x1cm, which were firm in consistency and mobile.

Patient was admitted for close observation and management, and was offered intravenous dexamethasone therapy.

Contrast enhanced computerised tomography (CECT) scan of the paranasal sinuses and the orbit revealed complete opacification with mucosal thickening of the left anterior ethmoidal air cells, frontal sinus and left maxillary sinus. Osteomeatal complex, left maxillary ostia, fronto-ethmoid recesses were opacified with tissue suggestive of obstruction. Overall features were suggestive of an infective aetiology, favouring osteomyelitis.

Local ultrasonography of the lesion revealed an ill-defined hypoechoic soft tissue lesion involving the left premaxillary region, left medial canthus and root of nose with peripheral vascularity. Bony irregularity involving the anterior wall of the maxillary antrum and left nasal bone were noted.

In the absence of clinical improvement during the first week of treatment, an ultrasound-guided fine needle aspiration cytology (FNAC) was performed from the nasal lesion which revealed non-specific inflammatory pathology. Concurrently, an excision biopsy of the enlarged right submandibular lymph node was performed, histopathology of which revealed multiple ill-formed granulomas with multinucleate giant cells and fibrosis. In addition, presence of micro abscesses with karyorrhectic debris surrounded by lymphocytes, plasma cells and histiocytes were noted. Focally, areas of vascular proliferation suggestive of vasculitis, were observed. Ziehl-Neelsen stain for acid-fast bacilli were negative. The biopsy was signed off as necrotizing granulomatous lymphadenopathy with the differentials of tuberculosis being favoured over Kikuchi's disease.

Based on the biopsy report and a pulmonary review, he was empirically started on antituberculosis treatment (ATT), but he failed to respond. On day 19 of admission, he became febrile, disoriented and demonstrated aggressive behaviour. Medical and psychiatric evaluation suggested maxillary sinus osteomyelitis, with a suspicion of central nervous system (CNS) tuberculosis. Magnetic resonance imaging (MRI) revealed multifocal non-haemorrhagic infarct secondary to embolic shower, possibly secondary to tuberculosis. (Fig 1A-1B) Cerebrospinal fluid (CSF) examination showed raised protein (106mg/dl) with sugar being 54mg/dl. Routine microscopy was paucicellular with 3 total nucleated cells/cumm, all being lymphocytes.

During this phase, apart from mild reduction in haemoglobin (11.6 mg/dl) and polymorphonuclear leucocytosis (11,400/cmm), all routine haematological, coagulation and biochemical profiles were within normal limits. Infective panel for hepatitis B and C, HIV, malaria, dengue, leptospira, SARS Cov-2, GeneXpert and culture for mycobacterium tuberculosis were negative. Screening for antineutrophil cytoplasmic antibody (ANCA) was also reported negative.

Managed protocol, however was modified to include antiepileptics, dexamethasone, vancomycin, ceftriaxone, acyclovir, magnesium sulphate and heparin, along with oral anti-tubercular medication. However, on day 23, his condition worsened and he was noticed to develop blackish ulcerative lesion on the medial canthus of the eye. Unfortunately, despite all efforts, on day 27 the patient succumbed to his condition.

Autopsy findings

A pathological autopsy was performed to identify the cause of death.

Gross examination of the CNS revealed an oedematous cerebrum with congested meninges along with 2 foci of liquefactive necrosis over the right frontotemporal and right temporoparietal regions (Figure 1C) measuring 2 x 1.7 and 1.5 x 1.3cm respectively. Right side parotid gland showed a whitish lesion measuring 0.5x0.5cm. The thoracic cavity revealed both lungs of normal size and shape with dull pleura showing multiple whitish nodules ranging from 1-2cm externally. (Figure 1D) Microbiological examination of the peritoneal fluid was positive for pseudomonas aeruginosa and candida species.

Histopathological examination displayed widespread vasculitis involving the cerebral hemispheres, (Fig 1E) lungs (Fig 1G) and the right parotid gland. (Figure 1H) The cerebrum revealed meningeal congestion along with areas of liquefactive necrosis, parenchymal oedema and leukocytoclastic vasculitis. In addition, pseudohyphae forms of fungal bodies were noted in the vessels which were highlighted by periodic acid-Schiff (PAS) (Figure 1 F) and Gomori Methanamine silver staining. Similar lesions were seen within the cerebellum as well.

The right parotid gland revealed a focus of coagulative necrosis with karyorrhectic debris along with dense mixed inflammatory cell infiltrate comprising of lymphocytes, neutrophils, plasma cells and macrophages. Occasional macrophages were seen engulfing nuclear debris. (Figure 1H) Vasculitis was noted.

Microscopic examination of the lungs revealed large areas of coagulative necrosis surrounded by karyorrhectic debris. The alveoli revealed the presence of pseudohyphae form of fungal organisms (Figure 1G) along with dense mixed inflammatory infiltrates comprising of neutrophils, lymphocytes, plasma cells and scattered eosinophils with focus of histiocytic aggregates. Features of vasculitis along with pulmonary oedema and haemorrhage were seen.

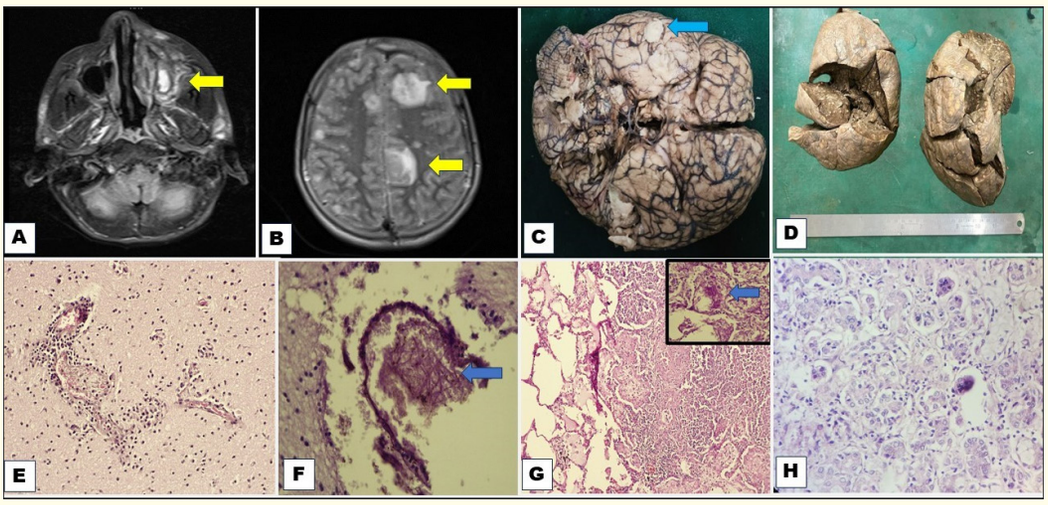

Figure 1: Post contrast MRI image showing maxillary sinus mass (A: arrow) along with foci of blooming in the cerebrum, suggestive of bleed. (B: arrow). Gross examination of the brain showed meningeal congestion along with liquefactive necrosis in temporoparietal region (C: arrow), while lungs showed dull pleura along with multiple yellowish white nodules ranging between 0.2 to 2 cm in size (D). Microscopic sections of the cerebrum revealed leukocytoclastic vasculitis (E: Haematoxylin and Eosin x 200), along with pseudohyphae form of fungal bodies (F: Periodic acid-Schiff x 400). Pulmonary sections displayed large areas of necrosis surrounded by karyorrhectic debris with alveoli containing entangled pseudohyphae of fungal organisms (G: Haematoxylin and Eosin x 200; inset: Periodic acid-Schiff x 400). Parotid showed focal coagulative necrosis along with karyorrhectic debris and mixed inflammatory cell infiltrate, with an occasional macrophage engulfing nuclear debris, depicted by arrow. (H: Haematoxylin and Eosin x 200).

Based on the histomorphological features and constellation of clinical symptoms the final cause of death was opined as multi-organ vasculitis with necrosis involving the lungs, parotid and cerebrum with mycosis of the lungs and cerebrum.

Discussion

This case presented a considerable clinicopathological dilemma. A constellation of clinical symptoms of nasal mass involving the periorbital region to involvement of the CNS due to non-haemorrhagic infarction was considered. This brought to light a wide

palette of aetiologies ranging from an initial impression of maxillary osteomyelitis with CNS tuberculosis to autoimmune conditions leading to the widespread vasculitis.

The primary question arose was the nature of the lynchpin event causing the nasal mass that culminated in a fatal outcome.

Initially being treated under the suspicion of osteomyelitis, parenteral corticosteroids were started with the aim of controlling the inflammation. However, the lack of response triggered a more detailed investigation. Based on the histomorphology of the biopsy, which favoured a possible tubercular lesion, patient was started on ATT, based on the NTEP guidelines.

The rapid deterioration of the patient along with CNS symptoms, warranted a pathological autopsy, since the underlying aetiopathogenesis was cofounding, and could be ascribed to a multitude of factors ranging from autoimmune to infections [12].

The macroscopic and histopathological studies lead to some interesting findings. Of note were the lungs, the cerebrum and the parotid gland with widespread leukocytoclastic vasculitis with karyorrhectic debris and macrophages seen engulfing nuclear debris. Another curious finding was that of presence of PAS-positive fungal pseudohyphae in the lungs and the cerebrum.

The features were suggestive of multi-organ vasculitis with widespread necrosis. Vasculitides are known to virtually involve any organ system as a pathological response to any kind of inflammation, be it immune mediated or due to direct invasion by infectious agents [1]. This along with the clinical presentation led to the suspicion of granulomatosis with polyangiitis (GPA) as one of the foremost contenders considered [2,3]. The small vessel vasculitis of GPA is known to be autoimmune with multiple triggers requiring but not necessitating confirmation with antineutrophil cytoplasmic antibody (ANCA) as a marker of autoimmune factor [4]. Further 2 of 4 criteria required for diagnosis by American College of Rheumatology: Positive biopsy for granulomatous vasculitis, urinary sediment with red blood cells, abnormal chest radiograph and oral/nasal inflammation were satisfied in this case [3].

The microscopic picture of the parotid initially presented a dilemma. However, a thorough review of literature suggested parotid gland involvement as one of the earliest signs of GPA further supporting our school of thought [7-11].

GPA almost fit the clinical picture presented. However, the age of the patient and the lack of signs of improvement despite long term corticosteroid administration [5,6] lead to us shelving GPA as our diagnosis whilst keeping this as an etiological differential.

Further evidence of fungus within the cerebrum and the lungs contributed to the diagnostic puzzle as necrotising vasculitis due to fungal infection is a known confounder of GPA [13]. The microscopic hallmark of both GPA and fungal infection is known to be vasculitis, parenchymal necrosis, and granulomatous inflammation, all of which were noted in this case [14].

As studied by Rice CM and Scolding NJ, the evidence of CNS angiitis (granulomatous, lymphocytic or necrotising) with evidence of vessel wall damage in the backdrop of clinical presentation suggestive of CNS vasculitis with exclusion of alternative possible diagnoses could be an indicator of cerebral vasculitis [15]. The study highlighted the importance of histological evidence of vasculitis to be the centre piece in the diagnosis of CNS vasculitis along with cerebral angiography in supportive role.

The evidence of necrotising and granulomatous cerebral angiitis along with the demonstration of fungal pseudohyphae on histopathology studies as well as isolation of fungal species of candida along with pseudomonas in postmortem peritoneal fluid microbiological culture clinched the diagnosis of widespread vasculitis with etiology contributed to mycosis. This correlated with the clinical history of eventual development of the blackish ulcerative lesion on the medial canthus of the eye, further contributing to fungus being the likely aetiology.

Bacterial infection of the nasal mucosa by Pseudomonas in association with superadded candida infection led to osteomyelitis of the paranasal sinus. Further events lead to vascular emboli leading to fatal non-haemorrhagic infarction. The clinical and initial antemortem histopathological investigations masqueraded as tuberculosis. Contributing to this was the abundance of varied atypical presentation of tuberculosis in our country thus making it the likely diagnosis given the demographic factors in this case [16]. Thus, a case of infectious vasculitis with mycosis ended up guising itself as tuberculosis.

Conclusion

Vasculitis and its sequalae, particularly vasculitis of the central nervous system, generally spell a poor prognosis for the patient hence warranting prompt diagnosis of the cause and institution of its management. A dialogue between the diagnostic branches and the clinicians is pivotal in this disease entity. Unlike its pulmonary counterpart, vasculitis in cerebral vessels is in need of more in- depth case reports and systemic reviews in order to establish a

definite practical diagnostic criterion as observed by Mcverry F., *et al*. [17]. Further, recognition of the importance of this entity along with large scale studies are needed to help in early and accurate diagnosis of the disease to improve prognostic outcomes.

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