Recently a syndrome of irreversible leukoencephalopathy has been reported in six children after allogeneic SCT, who received CSA for GvHD prophylaxis. These children exhibited progressive and continued severe neurological deterioration lasting for more than 2 weeks and consistent with non-localizing CNS abnormalities. For SCT recipients who develop CSA induced neurotoxicity alternative GvHD prophylaxis treatment is needed. Tacrolimus (FK506) and mycofenolate mofetil have been evaluated in such patients and found effective and relatively safe.

Our patient was receiving CSA along with steroids when he developed this complication. Initially CSA was restarted in low dose combined with mycofenolate mofetil. Later on CSA was totally replaced by mycofenolate mofetil due to CSA induced nephrotoxicity.

In summary CSA has multiple interactions with commonly used drugs beside its direct side effects like neurotoxicity and nephrotoxicity, which further potentiate its adverse effects. These drugs alter its metabolism leading to either dangerously high or low blood levels, which can render the drug either useless or toxic. Therefore, it is of paramount importance that when prescribing CSA with other drugs its interactions be kept in mind. We recommend that strict and regular monitoring of CSA levels is recommended in transplant recipients, particularly, when these patients are on multiple drugs during post-transplant follow up.

References

Case Report
Primary Aspergillosis of the Cheek. A diagnostic Dilemma
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Abstract
Primary cutaneous and subcutaneous aspergillosis is a rare entity and usually occurs secondary to systemic or disseminated aspergillosis. We describe a unique case of primary aspergillosis of the cheek in a 45 year old male without any evidence of disseminated aspergillosis and recognizable trauma or surgical procedure in the area of cheek.

Introduction
Cutaneous aspergillosis can occur as either primary or secondary infection. Primary cutaneous aspergillosis most commonly affects the exposed areas which get traumatized e.g. intravenous cannulation, venipuncture or any other penetrating injury. Other areas at risk are surgical or burn wounds which are covered with occlusive dressings. Cutaneous aspergillosis is seen only in 5-10% of patients with disseminated aspergillosis and occurs less commonly in the absence of trauma or haematogenous disease. Secondary cutaneous aspergillosis is seen secondary to contiguous extension of the lesion to the skin from infected underlying structures or blood-borne spread to the skin. Aspergillosis of the cheek is very rare and is generally associated with disseminated disease. We present a unique case of cheek aspergillosis without any history of recognizable trauma or evidence of disseminated aspergillosis.

Case Report
A 45 years old male presented with eighteen months history of gradually progressive firm swelling of left cheek associated with facial asymmetry. There was no history of facial trauma, dental infections or any other systemic illness. Patient was non smoker, normotensive and non diabetic. The patient had been visiting different hospitals for
management. Fine needle aspiration cytology (FNAC) was attempted three times but the results were inconclusive.

On examination the swelling was diffuse measuring 4x5 cm, firm and non tender. It was extending superiorly to the lower eye lid and laterally to the zygomatic arch. Overlying skin was intact but appeared slightly congested and had normal temperature. Clinically there was no involvement of the orbit (Image 1). Patient was afebrile and otherwise healthy. Oral examination showed good orodental hygiene. Cheek mucosa was normal. Nasal examination was unremarkable with normal nasal patency and intact sense of smell.

Haematological investigations were all within normal limits. X-Ray para-nasal sinuses occipitomental view showed opaque left maxillary sinus. CT SCAN was carried out which showed soft tissue density of left cheek. Anterior wall of the maxilla was intact and all paranasal sinuses including the maxillary sinuses were normal.

As previous FNAC reports were inconclusive we planned an excisional biopsy. A Standard Weber Fergusson's incision was used for surgery. On exploration, the swelling was present in subcutaneous tissue, 4x5 cm in size, pale white in color and firm in consistency. It was excised completely and submitted for histopathology. Patient had an uneventful post operative course. The histopathology revealed epitheloid cell granulomas. PAS staining was done which showed "septate hyphae within the granulomas" consistent with Aspergillosis.

The patient was put on antifungal treatment (Itraconazole) after consultation with Infectious Diseases' department. Patient responded well to the treatment and was followed up for three months without any evidence of residual disease or recurrence.

Discussion

Aspergillosis usually begins as a pulmonary infection subsequent to spore inhalation. In the immunocompromised host, haematogenous dissemination and invasion of other organ systems, including the skin, can follow the initial pulmonary infection. Isolated cutaneous and deep aspergillosis occurs rarely in the absence of disseminated aspergillosis or trauma. Patients at risk include Human Immunodeficiency Virus (HIV) infected individuals, patients on systemic steroids and other admitted/hospitalized patients. Commonest site of involvement, in these patients, is around the sites of intravenous cannulae protected by occlusive dressings. Various cases of primary or secondary cutaneous aspergillosis in non Human immunodeficiency virus (HIV) infected immunocompromised patients have been reported. These include neonates, burn victims, bone marrow and organ transplant recipients and cancer patients.

The diagnostic modalities of these lesions include imaging, serology, culture, Frozen sections and histopathology. Imaging studies such as CT scan and MRI are helpful in demarcation of the deeper lesions and the extent of involvement of adjacent structures. CT guided FNAC of deep lesions has a good diagnostic yield but has its limitations. Skin biopsy or FNAC of subcutaneous nodule with special staining for fungus, such as with methenamine silver or periodic acid-Schiff stains can be supportive or suggestive of Aspergillus infection, but other fungi may appear near identical in histopathologic sections. FNAC was done thrice on our patient without any diagnostic yield. CT scan only described the extent of the lesion and lack of involvement of the adjacent paranasal sinuses specially the maxillary sinus. Deep or disseminated
aspergillosis poses another diagnostic challenge as Aspergillus is a common laboratory contaminant. If truly present, tissue sections on histopathology show septate hyphae with acute angle branching found within the tissue.\(^6\) Primary cutaneous or deep infection is often associated with a granulomatous reaction and formation of multinucleated giant cells. The histopathology of the specimen of our patient showed similar findings of septate hyphae of aspergillus within the granulomas. (Image 2)

Although histopathology can detect aspergillus infection in the tissues its species cannot be confirmed. As newer antifungal agents are being developed there is a need for specification of the aspergillus subtypes. Aspergillus culture is used to detect the aspergillus subtypes. Aspergillus can be isolated in culture within 1-3 days but longer incubation times may be required if the inoculum is very small. However fungal culture may fail to detect aspergillus in 19-37\% of positive cases.\(^7,8\) In our case as the diagnosis was not suspected pre-operatively, the whole specimen was submitted in formalin. Therefore, we could not perform fungal culture for sub-typing of aspergillus species.

In disseminated or deep aspergillosis, serum galactomannan assay in conjunction with cultures and / or histologic examination can be used for diagnosis but it has limitations of having false positive and false negative results.\(^9\) PCR detection of aspergillus DNA is being developed as a new and very sensitive tool for the diagnosis and specification of aspergillus species.\(^7,8\) At present no facility for PCR detection of aspergillus subtypes is available in Pakistan and therefore, was not considered in our case.

All these diagnostic modalities are only helpful if a fungal infection is suspected. FNAC is diagnostic for aspergillosis but is highly operator dependent. Excision biopsy was done in our case only after three inconclusive FNACs. If there was any hint of fungal infection in the FNACs, a proper fungal culture could have been planned at the time of surgical excision.

Recommended treatment of primary aspergillosis, which has no evidence of extracutaneous aspergillosis, is the use of itraconazole.\(^10\) However, patients on itraconazole therapy should be monitored carefully for the response to treatment. In case of limited or no response itraconazole should be replaced with intravenous amphotericin B. In addition to antifungal treatment, adequate surgical debridement of extensive primary cutaneous lesions has shown to improve the clinical outcome. Newer liposomal amphotericin B has lower incidence of untoward reactions and has been used successfully in combination with voriconazole and micafungin to treat even the infants with cutaneous aspergillosis.\(^6\)

**Conclusion**

Unusual infections like primary aspergillosis of cheek are difficult to diagnose unless a high index of suspicion is used. Tissue culture for fungal infections must be considered in any atypical lesion on the body. In the near future PCR may become the most effective means of confirmation and the specification of fungal infections.

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**References**