Extensive actinomycosis with intracranial and mediastinal involvement: a therapeutic challenge

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SUMMARY
Central nervous system (CNS) involvement by actinomycosis is rare, seen in 2%–3% cases. It mostly spreads to CNS by haematogenous route from a distant primary site such as oral cavity, lung, abdomen or pelvis. Direct CNS extension can also occur. It mostly presents as brain abscess, meningoencephalitis, actinomycetoma, subdural empyema and epidural abscess. We report one case of extensive actinomycosis having intra and extraparenchymal CNS, spinal canal, retropharyngeal and mediastinal involvement. Due to such widespread extension and involvement of vital areas, complete surgical debulking was not possible. In addition to therapeutic resistance to conventional antibiotics, repetitive negative cultures posed significant difficulty in the case management.

BACKGROUND
Actinomycosis is a rare, slowly progressive, chronic suppurative granulomatous disease, caused by filamentous, gram-positive, non-acid-fast, anaerobic endogenous bacteria of the Actinomycetae family. Based on anatomical site of infection, they are classified into orocervicofacial, thoracic, abdominopelvic, central nervous system (CNS), musculoskeletal and disseminated forms, characterised by formation of multiple abscesses and sinus tracts that may discharge sulphur granules. The most common forms of CNS involvement are brain abscess (67%) followed by meningoencephalitis (13%), actinomycetoma (7%), subdural empyema (6%) and epidural abscess (6%). We report one case of extensive actinomycosis having intra and extraparenchymal CNS as well as spinal canal, mediastinal and retropharyngeal involvement.

CASE PRESENTATION
A male teenager presented to us with slowly progressive asymptomatic swelling over nape of the neck for last 7 years. It started as a small skin-coloured elevation over the nape of neck, which increased in size over the next 7 years to cover whole neck and adjacent scalp area. He also noticed few elevated lesions over this diffuse swelling that used to discharge reddish-yellow fluid intermittently. Patient experienced increasing difficulty in neck mobility, and mouth opening which compelled him to seek treatment. There was no history of discharge of grains/bony spicules, headache, fever, vomiting, seizure, focal neurological deficit or any other systemic reports. Patient did not undergo any dental surgery/procedure in the past. Patient used to assist his family in farming, which included carrying fodder and crops overhead.

His temperature was 37°C, blood pressure 98/64 mm Hg, pulse 124/min, respiratory rate 20/min and pallor was there on general physical examination. Lymph nodes were not palpable. Mouth opening was reduced to two finger width; dental hygiene was poor. Systemic examination was unremarkable.

Cutaneous examination showed large diffuse non-tender, firm to hard swelling over the nape of neck extending horizontally to the bilateral preauricular area (right > left side) and vertically from mid-occiput to lower neck without locally raised temperature. Swelling was studded with multiple papules and plaques with brown-coloured crusts and atrophic scars at few sites (figure 1). Swelling was fixed to underlying structures and overlying skin. Dimensions of swelling were 25 cm horizontally and 10 cm vertically. Rest of the mucocutaneous examination did not reveal any abnormality.

INVESTIGATIONS
Detailed investigations are given in table 1. Liver and kidney function tests, blood sugar, haemoglobin A1C and urine routine/microscopy were within normal range. HIV-ELISA, hepatitis B surface antigen and anti-hepatitis C antibody were negative.

Ultrasonography of neck showed an ill-defined heterogeneous soft tissue mass and thickening with multiple hypochoic areas with echogenic foci within, involving both subcutaneous tissue and intermuscular region. Multiple enlarged cervical lymph nodes were seen in bilateral level IB, II, III, IV and V region largest measuring ~1.1 cm in short axis diameter.

Non-contrast CT scan (NCCT) showed an ill-defined hyperdense mass along left temporal region with associated perilesional oedema and ipsilateral ventricular compression, dilated right lateral ventricle with mild midline shift to the right side. Marked hyperostosis and periosteal thickening involving left parietal, temporal, occipital bones were evident (figure 2). Contrast-enhanced MRI (CE-MRI) showed a large infiltrative lesion involving left hemicalvarium, a dural-based T1 isointense, T2 hypointense enhancing mass (with predominantly extraparenchymal and minimal intraparenchymal component) along left temporal lobe along with extensive pachy-meningeal thickening along the left cerebral hemisphere and cervical spinal canal. Significant perilesional oedema was seen in left temporal lobe. Mass was contiguous invading left
transverse and sigmoid sinus. Mass also showed retropharyngeal spread up to the superior mediastinum with cervical and upper dorsal vertebral body involvement. ‘Dot-in-circle’ sign was seen on MRI in the cervical soft tissues, which is typical of soft-tissue mycetomas (figure 3).

Audiogram was normal. Fibre optic laryngoscopy demonstrated adenoid hypertrophy, lateral and posterior pharyngeal wall showed bulge in oropharynx, vocal cords were bilaterally mobile. Ocular fundus examination was within normal limits. His cutaneous punch biopsy showed colonies of filamentous bacteria with surrounding Splendore–Hoeppli reaction and supplicative granulation tissue on H&E staining (figure 3).

### Table 1 Investigations and CSF investigations

| Investigations                  | Results                                      |
|--------------------------------|----------------------------------------------|
| Haemoglobin                    | 8.9 g/dL                                     |
| Total leucocyte count           | 8.36×10³/µL                                  |
| Differential leucocyte count    | 66/23/8/2                                    |
| Peripheral blood film           | Mild anisocytosis, microcytic hypochromic to normochromic red blood cells with poly-chromatophils and tear drop cells |
| Tissue fungal culture           | No growth                                    |
| Aerobic culture/sensitivity     | No growth                                    |
| Mycobacterial culture           | No growth                                    |
| Tissue anaerobic culture        | No growth                                    |
| Mantoux test                    | Negative                                     |
| HIV ELISA I/II                  | Non-reactive                                 |

| CSF examination                | Results                                      |
|--------------------------------|----------------------------------------------|
| Colour                         | Colourless                                   |
| Appearance                     | Clear                                        |
| Clot/coagulum                  | Absent                                       |
| Protein                        | 64 mg/dL                                     |
| Chloride                       | 124 Meq/L                                    |
| Glucose                        | 75 mg/dL                                     |
| Microscopy                     | WBC - 5 cell/mm³, RBC-32 cells/mm³, Cyto-spin smear, Pauci-cellular, few lympho-mononuclear cells, occasional neutrophils in a background of few RBCs, no malignant cell seen |
| Fungal culture                 | No growth (sterile) at 25°C and 37°C after 4 weeks of aerobic incubation |
| Aerobic bacterial culture and sensitivity | No growth after 48 hours of aerobic incubation |

CSF, Cerebrospinal fluid; RBC, Red blood cells; T1WI, T1-weighted image; T2WI, T2-weighted image; WBC, White blood cells.

Figure 1 Baseline clinical picture showing diffuse skin-coloured swelling present over neck; (A) right lateral view, (B) back view and (C) left lateral view.

Figure 2 Non-contrast CT scan of head and neck region. (A, B) Axial sections showing an ill-defined hyper-dense mass in left temporal region (black arrow) with associated perilesional oedema and ipsilateral ventricular compression. Dilated right lateral ventricle with mild midline shift to the right side. (C) Bone window showing marked hyperostosis and periosteal thickening (white arrow) involving left parietal, temporal, occipital bones. (D) 3D volume rendered image showing the surface irregularities of the involved bones due to hyperostosis.

Figure 3 MRI of the brain. (A) Axial T2WI showing a hypointense dural-based mass along the left temporal lobe with associated perilesional vasogenic oedema and thickening of ipsilateral skull bones (arrow). (B) Axial T2WI (magnified view) showing the dot-in-circle sign (arrows). (C) Coronal short tau inversion recovery (STIR) image depicting involvement of neck muscles and paravertebral soft tissues (arrow). (D) Axial, (E) coronal post contrast T1W images showing an enhancing dural-based mass with minimal involvement of the adjacent temporal lobe, marked enhancement of the dura along left cerebral hemisphere, and overlying scalp tissues (arrow) with infiltration of left sigmoid sinus (arrow in E). (F) Axial post-contrast T1WI image showing extensive enhancement of the cervical paravertebral muscles and tissues (arrow).
Gram-positive bacilli (figure 5B), while Gomori-methenamine silver (figure 5C), Periodic acid Schiff (figure 5D) & Ziehl-Neelsen stains were negative. Tissue aerobic, anaerobic, mycobacterial and fungal cultures were all negative and no microbial species identification could be done.

**DIFFERENTIAL DIAGNOSIS**

Differential diagnoses kept were actinomycosis, actinomycetoma, eumycetoma and tuberculosis looking at the triad of swelling with sinuses and grain discharge. Tuberculosis was ruled out on the basis of absence of related clinical symptoms, negative Mantoux test, normal chest X-ray, cerebrospinal fluid examination and negative sputum examination. Neoplasms were ruled out after CE-MRI and cerebrospinal fluid reports. ‘Dot-in-circle’ sign was seen on MRI, which is typically seen in soft-tissue mycetomas. Eumycetoma was ruled out after histopathological demonstration of filamentous bacterial colonies. Differentiation of actinomycosis and actinomycetoma was difficult due to negative culture reports and such atypical presentation, which is uncommon to both the entities. However, actinomycetoma being caused by aerobic species is easy to culture; the most common over feet, history of discharge of grains is always present both clinically as well as histopathologically and it is not known to invade CNS. In contrast, actinomycosis is more common in head and neck regions. Being secondary to endogenous anaerobic actinomyces species and polymicrobial nature of infection, culture reports are mostly negative, and discharge of grains is not as common as actinomycetoma. Thus, a diagnosis of actinomycosis was kept.

**TREATMENT**

Due to non-availability of first-line drugs (oral penicillin and intravenous crystalline penicillin), he was started on injection ceftriaxone 1.5 g × 3 weeks and oral penicillin G four lakh international-unit three times a day for 3 months. He had an improvement of about 20% after treatment (25 cm → 22 cm horizontally and 10 cm → 7 cm vertically). After completion of 3 months’ therapy of oral penicillin G, his swelling remained stable for next 3 months. But it started increasing again over next 6 months to reach the size more than baseline; 30 cm horizontally and 14 cm vertically.

Repeat CE-MRI showed an increase in the pachymeningeal thickening along left cerebral hemisphere and dural-based mass along left temporal lobe. Increase in retropharyngeal soft tissue component and extent of vertebral body involvement were seen with newer pachymeningeal thickening along the inferior orbital fissure, and newer involvement of left masticator space was noted; while mid-line shift had slightly decreased. Repeat tissue bacterial (aerobic and anaerobic) and fungal cultures were negative.

So, a revised diagnosis of actinomycetoma was made and he was put on intravenous injection amikacin 250 mg two times a day, oral rifampicin 300 mg/day and tablet cotrimoxazole 320/1600 mg, 1.5 tablet/day. Third, CE-MRI was done after giving this therapy for 20 days, which showed decrease in bulk and enhancement of calvarial disease, decreased pachymeningeal cervical spinal canal involvement, intraorbital extension along the inferior orbital fissure. But there was extensive increase in retropharyngeal, left masticator space involvement.

Considering the increased tissue extension of the disease even after 20 days of actinomycetoma regime, primary diagnosis of actinomycosis was retained. Patient was started on intravenous injection linezolid 600 mg/day and injection ceftriaxone 1 g three times a day for 42 days (6 weeks), as both the antibiotics have good CNS penetration and are efficacious against actinomy- cosis. In between this 6 weeks’ regimen, patient was also put on steroids as suggested by neurologist. His swelling decreased drastically with addition of intravenous injection of dexamethasone 6 mg three times a day within 7 days. Doses of injection...
dexamethasone 6 mg were tapered weekly from three times to two times and one time a day, along with addition of increasing dosage of oral prednisolone.

Patient was planned for discharge on oral penicillin G four lakh IU BD, after completion of 6 weeks of intravenous ceftriaxone and linezolid. On the night before discharge, patient deteriorated. He developed sudden-onset vomiting, headache and disorientation along with decreased mouth opening to one finger width. Urgent NCCT head was done, which showed increased vasogenic oedema in the left parietotemporal region with new development of hydrocephalus and cerebral oedema. As suggested by neurosurgeon, injection Mannitol intravenous 100 mL was started urgently. Next morning, MRI brain with angiography highlighted slight increase in white matter oedema in left occipital region and midline shift to right with effacement of sulcal spaces as compared with previous scan (8.4 mm at as compared with 6.4 mm) without any evidence of frank abscess within brain parenchyma. Patient’s vomiting improved next morning but headache and disorientation persisted. Mannitol was continued at three times a day for 3 days, along with the addition of tablet furosemide (20 mg)+spironolactone (50 mg), ½ tablet two times a day and injection dexamethasone 6 mg two times a day (5 days). This led to recovery of headache and disorientation. Patient then turned out COVID-19 positive, but his SpO2 was maintained at 100% and chest was clear. Mannitol was then tapered to two times a day for 2 days then to one time per day for 3 days, and then stopped. Injection doxycycline 100 mg two times a day and injection clindamycin 600 mg intravenously three times a day for 1 week were given to the patient. Patient was discharged after complete stabilisation.

He was discharged on weekly tapering dosage of tablet prednisolone (40 mg to 10 mg), tablet penicillin G four lakh IU two times a day, capsule doxycycline 100 mg two times a day and tablet metronidazole 400 mg three times a day. Along with this, he was prescribed, tablet furosemide (20 mg)+spironolactone (50 mg) ½ tab two times a day for 7 days, syrup glycerol 30 mL three times a day for 7 days, and monitoring of blood pressure and sugar every alternate day.

OUTCOME AND FOLLOW-UP

Patient came to us for follow-up after 1 month of discharge. His swelling had decreased on follow-up to 60%. He has been given oral penicillin G, doxycycline, metronidazole and prednisolone 5 mg on this follow-up visit. Marked reduction in swelling has occurred after 4 months of oral therapy (figure 6).

Figure 6  Clinical image showing markedly reduced swelling after 4 months of oral therapy; (A) right lateral view, (B) back view and (C) left lateral view.

DISCUSSION

Actinomycosis is caused by anaerobic endogenous bacteria of the Actinomycetaceae family. It requires the presence of other accompanying bacteria along with mucosal disruption, to cause disease. Almost all actinomycotic infections are polymicrobial and the accompanying bacteria reduce the oxygen concentration in infected tissues, inducing the ideal anaerobic conditions for the survival of Actinomyces.

CNS involvement by actinomycosis is rare, seen in about 2%–3% of cases. It mostly gets involved by haematogenous route from a distant primary site such as the oral cavity, lung, abdomen or pelvis. Direct CNS spread can also occur through invasion via head and neck area. Most common intracraniain presentations are brain abscess (67%) followed by meningencephalitis (13%), actinomycetoma (7%), subdural empyema (6%) and epidural abscess (6%). Frontotemporal lobes are most frequently involved by brain abscess. Actinomycosis of CNS can present with hemiparesis, focal or generalised seizures, headache and other features of raised intracranial pressure and space-occupying effects. Leucocytosis may be detected on routine investigations. Other acute phase reactants may be normal or mildly elevated. Our case remained clinically asymptomatic for prolonged phase and his laboratory work-up did not reveal any significant change.

Actinomycosis with dural-based masses is frequently misdiagnosed preoperatively as meningiomas with dural tail. So, identification of ‘Dot-in-circle’ sign on MRI in associated soft-tissue component as in our case is a helpful clue to rule out neoplastic aetiology. The dura mater has acted as a tight barrier in this case against the bacterial invasion for a very long period. The absence of neurological symptoms and significant CSF findings in this case despite temporal lobe oedema and midline shift can be explained by the slow-growing nature of infection as is evidenced by marked perioveal reaction along the involved calvarium and dura mater acting as a barrier. The perilesional oedema in temporal lobe in our case was due to the additive effect of large dural-based component of the mass along with thrombosis of the left transverse, sigmoid sinuses. Isolated thrombosis of the venous sinuses would have resulted in lesser extent of perilesional oedema.

Cutaneous actinomycotic infections are extremely rare and mostly result from wounds that were contaminated with saliva or dental plaque material, either by human bites or as a consequence of fist-fight trauma. Haematogenous spread to the skin from a distant primary site has also been observed. The clinical picture of these cutaneous actinomycoses is very similar to that of the cervicofacial form. There is hardly any report of cutaneous actinomycosis of occipital scalp leading to CNS invasion directly.

Culture reports though definitive of diagnosis are negative in upto 70% actinomycoses. Thus, presumptive diagnosis mostly relies on histopathological presence of gram-positive filamentous organisms and sulphur granules. As actinomycosis is a polymicrobial infection, the synergistic bacteria are frequently detected in culture and mask the growth of actinomyces. Penicillin G is the drug of choice regardless of the severity and site of actinomycosis. Milder infections can be treated with 2 months’ course of oral antibiotics while more severe and complicated cases need surgical debriement along with high dose of antibiotics for prolonged duration due to poor penetration of drugs into fibrotic tissues.

Intravenous penicillin (18–24 mU/day, given in divided doses every 4 hours) for 4–6 weeks followed by oral therapy
Case report

Patient’s perspective

For the last 7 years, I had noticed a swelling over the nape of my neck. It was gradually increasing in size. I did not pay much attention to it, considering it a general boil and thought that it would subside on its own. For the first 4 years I visited faith healers and paramedics. They used to give me some medications, but the swelling kept on increasing. Gradually, me and my family noticed that it is decreasing my neck mobility and mouth opening. Chewing and eating food became increasingly difficult. Me and my whole family got scared that it might be some tumour and extend to the brain. Then we started going to hospitals. I used to get many drugs, but my swelling remained unchanged or kept on progressing.

Then, I was referred to my current hospital by some of our villagers. Treating consultant there showed great interest in my disease. He told me about my disease that it is not a tumour but an infection may be fungal or bacterial in nature. He ordered many blood investigations for my initial visits without diagnostic confirmation and definitive treatment. I used to feel hopeless and lose my hope of surviving after such exhaustive investigations where I used to spend whole days in hospitals running from one room to other. My family members were rather more stressed because of their stay along with me in the hospital, we were losing our daily wages, our farming work was getting affected which were the only source of our family income. The consultant doctor told me, ‘confirmation of infection could not be done but MRI is showing extension of infection to the brain, so we need to start treatment as early as possible’. This made me and my family even more stressed. We thought that he is hiding some big serious disease from us, just not to disappoint us. His attitude was very polite and positive. The consultant doctor, all the out-patient department, ward staff and resident doctors used to treat me very well. They used to make me smile even on my saddest days. They never left me alone with my thoughts and boosted my moral. Because of their such personal emotional touch, I gained hope. Doctors started me with some drugs. I took the drugs for 3 months and my swelling started to decrease. I was very much delighted, as for the first time after 6 years, my swelling was decreasing and I was able to start to decrease. I was very much delighted, as for the first time after 6 years, my swelling was decreasing and I was able to

being diagnosed with COVID-19 and moving to the COVID-19 ward. We were scared of contracting COVID-19. But most of the doctors were very friendly and jolly-natured people. They always used to keep the mood light. Doctors used to come everyday with the same enthusiasm. Sometimes, I used to feel, they were more worried about my disease than me. This enthusiasm was the reason that kept my survival hope alive. They arranged for my good health; physiotherapy sessions, nutritionist and psychiatrist, to keep me healthy and motivated. Over the time I stopped missing my home, family and friends. There came a time when I lost hope when I got an episode of vomiting and headache. But the team of doctors there did not give up. They never watched clock whenever I needed. I had seen many of them missing their breakfast, lunch, dinner and sleep many times for me. I lost hope of surviving many a times and wanted to run away to spend my last days of life at home. I used to miss food made by my mother. Then, the day came when my injectable drugs’ course got completed and I was fit for discharge. I was given many drugs to be taken orally. I strictly adhered to the treatment course this time as these doctors had put so much efforts into curing me. I wanted to be perfectly alright this time. I have been taking the drugs for 4 months now after discharge and my swelling has decreased a lot. I feel like a huge mountain has been unloaded from my head. I can eat, play, move and dance with with my friends. I can wear non-collared clothes now comfortably. I will always be thankful to the doctors and staff who cared for me like their own family members.

Learning points

► Actinomycosis of head and neck area is easily confused with actinomycetoma, which are not synonymous. Actinomycosis is an endogenous anaerobic infection while actinomycetoma is an exogenous aerobic infection by filamentous bacteria of actinomycetaceae family.

► This was a rare case of extensive central nervous system actinomycosis where complete surgical debulking was not possible due to widespread extension to intracranial, spinal canal, mediastinal and cervical structures.

► A multidisciplinary team approach helped us to direct and achieve appropriate management.

► Effective teamwork and communication between pathologist, microbiologist, radiologist, neurologist, neurosurgeon, otorhinolaryngologist, ophthalmologist and oromaxillofacial surgeon is required for management of such difficult cases.

with penicillin (1–2 g/day in divided doses every 6 hours) or amoxicillin (1.5 g/day in divided doses every 8 hours for as long as 6–12 months) is a reasonable clinical guideline. Other drugs which have been found to be effective in actinomy- cosis are erythromycin, clindamycin, imipenem, ceftriaxone, ciprofloxacin, cefepime, linezolid, meropenem and vancomycin. Actinomyces is an endogenous anaerobic infection while actinomycetoma is an exogenous aerobic infection by filamentous bacteria of actinomycetaceae family.３,４ Doxycycline can be given for prolonged periods (6–12 months) following initial course of intravenous antibi-otics.３,４ Metronidazole, trimethoprim-sulfamethoxazole, cefazidime, aminoglycosides, oxacillin and fluoroquinolones are not active against the bacteria; they can be used as addi- tional agents to cover other aerobes and anaerobes in mixed infections based on the culture and sensitivity reports.３ Apart

Continued
from antibiotics, patient may require symptomatic management such as antiepileptics for prolonged periods. Course of steroids may be required in tapering doses for control of acute inflammation and seizures. Surgery is reserved for brain abscess, refractory disease and involvement of critical sites.

Peculiarities of our case were as follows: direct CNS spread from subcutaneous swelling rather than haematogenous spread from a distant site, patient was apparently asymptomatic for very prolonged period with absence of neurological symptoms, involvement of CNS was in the form of a dural-based mass with minimal parenchymal involvement, dural venous sinus invasion, spinal canal pachymeningeal involvement, mediastinal, orbital wall and retropharyngeal spread rather than commoner presentations, and occipital region was predominantly involved rather than frontotemporal regions.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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