Case report

Massive progressive scroto-perineal eumycetoma and its therapeutic challenges.

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Case 1

A 57 year-old male, from central Sudan, presented to the Mycetoma Research Centre (MRC), Khartoum, Sudan, with a slowly progressive right inguino-scrotal swelling of 35 years duration. He also reported local scrotal pain and itching. The swelling was first noted in 1982 as a small painless mass in the lower inner quadrant of the right gluteal region. By 2005, it progressively increased in size and a purulent discharge containing black grains appeared. The patient did not recall any history of local trauma. He underwent surgical excision under local anaesthesia at a regional hospital. Two years later he developed local recurrence that extended to the perineal area just below the scrotum that started to discharge pus and black grains. He underwent further surgical excision under spinal anaesthesia. However, following these surgical excisions, no tissue diagnosis was established, and no treatment was given.

In 2010, he presented to the MRC complaining of right hemiscrotal painless swelling of six months duration. Clinical examination revealed a mass measuring 5×4 cm, with multiple sinuses discharging pus and black grains; it was soft in consistency and was attached to the skin and deep structures. The diagnosis of *Madurella mycetomatis* eumycetoma was established by cytological examination of fine needle aspirate from the lesion.

He was commenced on 200mg ketoconazole twice daily orally and folic acid 5 mg once a day orally. Two months later he underwent wide local excision at the MRC under spinal anaesthesia. He remained inpatient for 45 days for daily wound dressing and was discharged in good condition. He then had reconstructive plastic surgery to cover the open wound by a skin graft.

A follow-up ultrasound examination three months later identified local recurrence. Sadly, he stopped taking his medications due to social reasons. In 2013 he presented to the MRC with local recurrence, and the lesion ultrasound examination revealed right testicular invasion. He was commenced on 200 mg itraconazole twice daily orally, and folic acid tabs 5 mg once a day; however, the swelling did not regress in size with treatment.

Four years later, in 2017, the patient noticed a rapid increase in the swelling, which extended to the right inguinal region. Seven months prior to his presentation, he developed scrotal pain and itching, which was of low grade and mainly nocturnally. He had no constitutional symptoms.

The patient is diabetic on 500mg metformin twice daily for four years. He was not on other long-term medication. He has a family history of mycetoma; his brother had a right foot eumycetoma. He worked as a cashier, married with 12 children and the youngest is 12-year-old.

On clinical examination, the patient looked well, neither pale, jaundiced, nor cyanosed. He had no

difficulty in walking. Local examination revealed massive swelling at the right inguinal region and the right hemi-scrotum with no superficial dilated veins. There were multiple active sinuses discharging pus, blood and black grains. It was not tender on palpation. It was soft in consistency, not mobile and was attached to the skin. Fluctuation test was negative. Transillumination test was negative, (Figure1).

Figure 1. The scrotal swelling with multiple active sinuses discharging pus, blood and black grains.

A complete blood count showed leucocytosis with total white blood cells counts (TWBC) of 12.100 cells/ml, a low haemoglobin concentration of 6.6 g/dl, and thrombocytosis (532.000/dl). Random blood glucose level was 171 mg/dl. A swab was collected from the sinuses for culture and drug sensitivity, but no organism was isolated. Renal and liver profiles were normal. Grains were collected for culture and a polymerase chain reaction (PCR), and it was positive for *Madurella mycetomatis.*

The Interleukin IL-12 and IL-4 levels were measured by ELISA test. IL-12 concentration was higher compared to the healthy control sample ($p < 0.01$) while IL-4 was decreased significantly compared with the healthy control sample ($p < 0.01$). Interleukin (IL)-12 links the innate immunity with the development of adaptive immunity and is also important for regulating T cell responses, and it was reported to be important during systemic infection. Interleukin (IL)-4 is a type-2 response that elicits the production of non-opsonizing antibodies and allergic reactions and down regulates the extensive inflammatory reaction caused by Th1 cytokines.

Abdominal and pelvic ultrasound examination showed multiple connected pockets of fluid containing grains associated with right scrotal hydrocele, (Figure 2).

Figure 2. Scrotal ultrasound examination showing multiple connected pockets of fluid containing grains and right scrotal hydrocele.

Pelvic X-ray excluded bone involvement. Two months later MRI revealed that the mycetoma had invaded of the right epididymis and ascended along the spermatic cord and ended proximally at the level just below the tubercle of the right pubic bone with the involvement of the posterolateral aspect of the right hemiscrotum, the scrotal septum. No detectable lesion was seen in the left hemiscrotum and the urogenital triangle, (Figure 3).

On 8th of February 2018, the patient underwent wide local excision of the right hemiscrotum with excision of the right testis and epididymis under spinal anaesthesia with uneventful postoperative recovery. He was followed at the out-clinic, but he was lost for follow up.

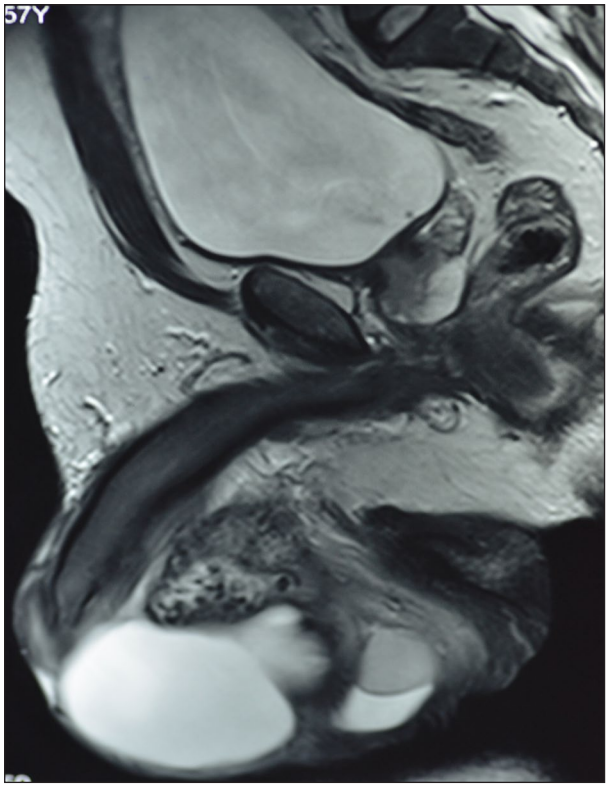

Figure 3. MRI showing mycetoma invading the right epididymis, ascending along the spermatic cord ending proximally at the level just below the tubercle of the right pubic b one with the involvement of the posterolateral aspect of the right hemiscrotum and the scrotal septum.

Case 2

A 34 year-old male, from the central part of Sudan known case of scrotal and perineal *Madurella mycetomatis* eumycetoma was recently seen at the MRC. He was first seen and diagnosed at the MRC four years previously, but he was not on regular follow up at the centre. At presentation, he had a painless large inguinal swelling extending to the left hemi-scrotum. The condition actually started in 2007 with painless small swelling in the left gluteal region that gradually increased in size. He has no history of local trauma. He underwent several wide local surgical excisions in 2009, 2010, 2011 and another two excisions in 2017. All previous surgeries were done under spinal anaesthesia and were uneventful without complications. The patient has neither a family history of the same condition nor other conditions. He was not on long-term medication apart of oral 200mg itraconazole twice a day and folic acid 5 mg once a day for his eumycetoma. There is no history of allergy or other co-morbidity. The patient is a freelancer worker of low socioeconomic status. He is married with two children; five and three years old. The systemic enquiry was unremarkable.

On examination, he looked well, and had no difficulty in walking. His blood pressure was 120/70 mmHg, pulse rate 60 b/min and respiratory rate was 22 breath/min. Systematic clinical examination revealed no abnormality. Local examination revealed a long surgical scar extending obliquely along the left lower half of the gluteal region extending into the inner aspect of the left perineal region, (Figure 4A &4B). The patient has an extensive swelling involving the perineal region spreading to the left hemi-scrotum with multiple sinuses discharging offensive pus and black grains. The swelling was firm in consistency, not tender with normal temperature, not mobile and was attached to the skin. Fluctuation and trans-illumination tests were negative. There were no palpable inguinal lymph nodes and no superficial dilated veins.

Figure 4A. the long surgical scar is extending obliquely along the left lower half of the gluteal region into the inner aspect of the left perineal region.

Figure 4B. Showing an extensive swelling involving the perineal region spreading to the left hemiscrotum with multiple sinuses.

MRI showed a mass occupying the left perineal fat tissue and mildly extending to the right side and also involving the left side of the scrotum, and the gluteal region (Figure 5A & 5B). Grains PCR examination revealed *Madurella mycetomatis.*

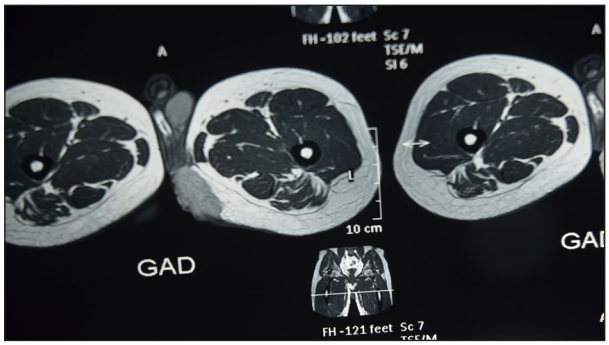

Figure 5 A. MRI showing a mass occupying the left perineal fat tissue and mildly extending to the right side and gluteal region.

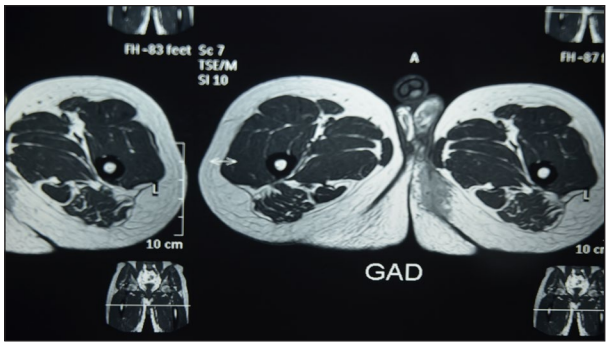

Figure 5B. MRI showing the swelling involving the perineal and left side of the scrotum.

The patient was admitted to the hospital. A complete blood count showed TWBCs count of 6000 cells/ml, with normal differential parameters, haemoglobin of 14.8 g/dl, normal platelets count. Random blood glucose level was 92 mg/dl. Renal function revealed urea of 16 mg/dl, creatinine of 0.9 mg/dl, Na^+ of 139 mmol/l and K^+ of 3.8 mmol/l. Viral screening for HBV, HCV and HIV were non-reactive. A swab was collected from the sinuses discharge for micro-organisms culture, and antimicrobial agents' sensitivity revealed the growth of *Escherichia coli* which was sensitive to Cefuroxime of which he received 750 mg three times a day for two weeks.

He was started on oral 200 mg itraconazole twice daily and folic acid 5mg once daily. He underwent wide local excision and left orchiectomy. The wound was closed primarily, and he had uneventful postoperative recovery. He is not on regular follow up now.

DISCUSSION

Mycetoma is an unparalleled, devastating neglected tropical disease caused by several microorganisms of fungal or bacterial origin.[1] Hence it is classified as eumycetoma and actinomycetoma, respectively.[2] It is endemic in many tropical and subtropical countries and Sudan seems to be the mycetoma homeland.[3] The geographical distribution of mycetoma depends on certain environmental factors such as rainfall, humidity and temperature.[4] Mycetoma frequently affects the extremities; the foot and hand.[5] Less commonly affected sites include the leg, knee, chest wall, head and neck.[6,7,8] An extensive review of the medical literature had revealed few reported scrotal mycetoma patients.[5,9]

In this communication, both patients had eumycetoma caused by *Madurella mycetomatis,* which is the commonest causative organism in Sudan.[10] Mycetoma is believed to occur as a result of traumatic implantation of the causative organism into the subcutaneous tissue via minor trauma or injury.[11] However, both patients denied a history of local trauma at the mycetoma site. It may be minor injuries passed unnoticed. In the poor

rural community, due to water shortage and poor socioeconomic and health education levels, some people use soil to clean themselves after defecation, and that may be an important mechanism for the causative organism inoculation for scrotal and perineal mycetoma.[5]

Both patients had the mycetoma pathognomonic triad of the painless subcutaneous mass, multiple sinuses, and purulent or seropurulent discharge containing coloured grains.[1,2,3] The painless nature of the disease is likely to be an important cause for the late presentation of these patients. Furthermore, many patients if developed medical problems in the genital regions do not present early for medical advice as that is considered as a social stigma in many communities in Sudan and that may also be the cause of the late presentation of the patients reported here.

In mycetoma, the external appearance is always deceiving and misleading, as seen in the reported patients. Both of them had an extensive inguinoscrotal invasion and few cutaneous signs. Hence, surgery under local anaesthesia is contraindicated as wide local surgical excision is frequently incomplete. Suboptimal excision is always associated with local recurrence and sometime with distal spread.[12] This was evidenced in the reported patients. A tourniquet bloodless field surgery is mandatory in mycetoma for adequate wide local excision, and this was not feasible in these patients and thus the multiple recurrences.[12] The complexity of the scrotal, perineal, gluteal and inguinal anatomy always makes radical surgical excisions incomplete and can contribute to the high recurrences seen in these patients.[12]

It is interesting to note in spite of the long-standing extensive disease in the inguinal, perineal and scrotal regions the patients were sexually active. The first patient had 12 children, and the second one had two. It is interesting to note although the disease had deeply invaded the deep tissue, the hip joints were not involved, and their gaits were normal.

In the first patient, the cytokine IL-12 level was significantly increased compared to healthy controls. Nevertheless, the patient had a significantly lower level of IL-4. The study results suggested that cytokine responses induced by *Madurella mycetomatis* during the course of infection may play an important role in the differences in the pathogenicity. It seems likely that the antifungal treatment might have exerted immunomodulatory effects through the increase of the pro-inflammatory cytokine IL-12 and the decrease in the anti-inflammatory cytokines IL-4. Unfortunately, only a small fraction of cytokines was tested in this study, thus more Th1 and Th2 cytokines should be further assessed in those patients for a better understanding of the disease pathogenesis.

The reported patients are of low socioeconomic status and health education level, and they came from remote rural areas with scarcity of medical and health facilities. They were operated on by poorly trained medical assistants under local anaesthesia in low-resources medical centres. This would have contributed to the high recurrence rates encountered among these patients. In spite of the multiple surgical excisions, no surgical biopsies were taken, and no diagnosis was established. To avoid this poor practice, objective training of general practitioners and medical assistants, particularly in mycetoma endemic areas is mandatory and is currently being pursued.[13]

A careful preoperative assessment of the disease extension among the different tissues planes is always essential to plan the type of surgery.[14] MRI proved to be useful and accurate in determining the disease extension.[15]

Many mycetoma patients require reconstructive plastic surgical treatment following the lesions wide surgical excision. Thus it is helpful to have a plastic surgeon as part of the multidisciplinary team. In mycetoma, the open surgical wounds need special attention, necessitating hospital admission for proper wound care, daily dressing under aseptic conditions using appropriate dressing solutions and dressing material and infection surveillance with

frequent swab culture and antibiotic therapy when required.

These two cases of scroto-perineal eumycetoma illustrate the management and therapeutic challenges and the importance of a multidisciplinary team in the management of mycetoma patients.

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