CASE REPORT

Noma in a child with acute leukaemia: when the 'face of poverty' finds an ally

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SUMMARY

A 2-year-6-month old, appropriately immunised, well-thriving boy, symptomatic for the past 6 months, presented with recurrent fever, progressive pallor, lymphadenopathy and a raw area on the right cheek, with discharging sinus. The necrotising infection of the face developed after one and half months of febrile illness. This febrile illness with bicytopenia was diagnosed as enteric fever and treated with antibiotics. Skin grafting was performed for the full-thickness defect of the face. The patient continued to have a non-healing oral ulcer with progressive pallor and was finally diagnosed as having acute lymphoblastic leukaemia. Immunodeficiency was ruled out by appropriate investigations. Noma is an indirect measure of extreme poverty, but malignancy is known to predispose to this debilitating condition. The worldwide incidence of Noma is reported to be 30 000–140 000, with a preponderance in sub-Saharan Africa. This case emphasises the need for a thorough search for the underlying illness predisposing to a rare opportunistic infection such as Noma in a well-thriving child.

CASE PRESENTATION

A 2-year-6-month old, appropriately immunised boy, symptomatic for the past 6 months, presented to us with recurrent fever, progressive pallor, lymphadenopathy and a raw area on the right cheek, with discharging sinus.

The child developed the facial lesion after 1½ months of onset of fever. The lesion started as an oral ulcer associated with redness over the cheek, which progressed to the neck. Investigations revealed leucopenia and thrombocytopenia (total leucocyte count (TLC) $3.2 \times 10^3/\text{L}$ and platelet count $82 \times 10^3/\text{L}$). A possibility of malignancy was considered in view of bicytopenia, and the child was investigated for underlying malignancy. Fine-needle aspiration cytology of the submandibular gland was inconclusive and bone marrow was hypocellular with no evidence of malignancy. Therefore, diagnosis of enteric fever (Widal test positive with *Salmonella typhi* O and H titre 1:160) was made and the patient was treated with a parenteral antibiotic (ceftriaxone). Packed red blood cell transfusion was also given for anaemia. The fever responded transiently but the child developed swelling over the right cheek region with worsening of buccal ulcer. There was a rapid progression of the lesion to involve the orbit and neck region with erosion of overlying skin. The disease had a fulminant course with necrosis of the surrounding soft tissue and gangrene formation.

The child was referred to a higher centre for further management.

On presentation to the referral Centre, the child was noted to have a raw area, measuring about 15×6 cm, over the right side of the face, extending from the right temporal region superiorly, to the right angle of the mandible inferiorly, involving the right nasolabial fold medially and laterally up to the pre-auricular area. The full-thickness defect was noted on the lateral part of the right cheek 1 cm from the right oral commissure, with alveolar and dental exposure. Haemogram at the time revealed haemoglobin (Hb) 108 g/L, TLC $11.3 \times 10^3/\text{L}$ and platelet $164 \times 10^3/\text{L}$; culture of the wound showed growth of *Enterococcus* spp sensitive to linezolid and chloramphenicol. With the diagnosis of cancrum oris, the child was continued on broad spectrum parenteral antibiotics and underwent debridement and skin grafting of the right cheek with delayed primary closure of the neck wound. There was graft uptake in 90% of the area, but he developed an orocutaneous fistula (figure 1). Bone marrow slides were reviewed and found to be inadequate for opinion. The child remained relatively asymptomatic for the 2 months following the control of local infection, but continued to have low-grade fever and pallor, so the parents brought the child to our centre.

After admission at our centre, the child was noted to have pallor with submandibular lymphadenopathy, and oral ulcer with sequelae of Noma on the right side of the face. His weight and height were above the third centile for age and gender, with no organomegaly. The possibility of primary and secondary immunodeficiency, malignancy and autoimmune diseases was considered, and investigations were carried out accordingly.

INVESTIGATION

The child had Hb of 91 g/L TLC $6.4 \times 10^3/\text{L}$ and platelet of $69 \times 10^3/\text{L}$ with no abnormal cells on peripheral smear. Liver and renal function tests were normal. Immunoglobulin (IgG, IgA, IgM and IgE) levels were normal for age and Nitro blue tetrazolium test was positive, ruling out chronic granulomatous disease. Secondary immunodeficiency due to HIV was also ruled out. There was evidence of right maxillary sinusitis on imaging, but samples obtained from antral lavage did not grow any organism in culture. Blood cultures were negative. Bone marrow aspiration showed 60% MPO negative blasts (figure 2) and flow cytometry revealed 30% blasts positive for CD19, CD 45, CD34 and cCD79a; bone marrow cytogenetic studies were normal.

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Figure 1 Sequelae of Noma showing full-thickness defect of right cheek with orocutaneous fistula.

DIFFERENTIAL DIAGNOSIS

Our case had long-standing illness with pallor, lymphadenopathy, thrombocytopenia and persistence of oral ulcers. Malignancy was suspected initially at the referring centre, but was dismissed in view of the normal report of the bone marrow examination, which was actually inadequate for opinion. The child's condition was attributed to enteric fever based on laboratory results, as enteric fever is known to predispose to Noma. The differentials for orocutaneous lesions of Noma include mucocutaneous leishmaniasis, lupus erythematosus, leprosy, agranulocytic ulcerations, physical trauma and burns, also,

Figure 2 Photomicrograph of bone marrow aspirate showing infiltration by lymphoblast.

syphilis immunodeficiency was considered in view of the unusual infection and an unusually prolonged course. A primary T-cell defect was unlikely as the child was thriving well, with no history of recurrent multisite infection, and the onset of illness was at 2 years of age. Normal immunoglobulin levels ruled out a primary B-cell defect. Secondary immunodeficiency was a likely possibility. Apart from HIV infection, poor nutritional status and underlying malignancy also predispose to opportunistic infections. Presence of thrombocytopenia with progressive pallor was a pointer towards underlying bone marrow involvement, and bone marrow examination proved the diagnosis of acute leukaemia.

TREATMENT

The child was started on empirical broad spectrum antibiotics for the underlying sinusitis and non-healing oral ulcers, and chemotherapy was initiated after confirmation of acute leukaemia on bone marrow examination. He responded well to four drug induction (prednisolone, L-asparaginase, vincristine and daunorubicin) chemotherapy. He became afebrile with no recurrence of cheek swelling and oral ulceration after recovery from chemotherapy-induced bone marrow suppression.

OUTCOME AND FOLLOW-UP

The bone marrow was documented to be in remission postinduction chemotherapy at 1 month. The child is presently undergoing consolidation chemotherapy and reconstructive surgery is planned for the sequelae of Noma after completion of chemotherapy.

GLOBAL HEALTH PROBLEM LIST

Noma is seen exclusively in low income countries with high prevalence of poverty and malnutrition.

The high incidence of malnutrition in the Indian subcontinent can predispose to many opportunistic infections including Noma.

Poverty, malnutrition and debilitating illnesses are central to the pathogenesis of Noma.

Lack of awareness among healthcare professionals of the association of this devastating illness with malignancy may delay the diagnosis.

There is a lack of epidemiological surveillance and global monitoring system for reporting of Noma cases.

GLOBAL HEALTH PROBLEM ANALYSIS

NOMA—a disease of poverty

Noma is derived from the Greek word, 'to devour'; Noma is also known as orofacial gangrene, necrotising ulcerative stomatitis, stomatitis gangrenous or cancrum oris. It is a fulminant infection of oral facial tissue, leading to the rapid destruction of orofacial and adjacent structures, with a high mortality rate of 70–90% in the absence of prompt treatment.¹ Noma has been called the 'face of poverty'.² The peak incidence of Noma is between the ages of 1–4 years.³ Poverty, malnutrition and debilitating illness are considered to be central to the pathogenesis of Noma. Worldwide case estimates range from 30 000 to 140 000.³ Cases are mainly reported from sub-Saharan Africa, considered to be the Noma belt. It is virtually non-existent in developed countries. Measles, scarlet fever, typhoid, tuberculosis and leukaemia are known predisposing illnesses. The Indian subcontinent has a high incidence of malnutrition, but for some unknown reason, Noma is not frequently seen.⁴ Noma, in association with malignancy, is found in only a few

case reports in adult patients, with only one report in an adolescent.

Factors predisposing to Noma

Poverty, malnutrition, poor oral hygiene, residential proximity to livestock in unsanitary environments, and infectious diseases such as measles and herpes virus, all contribute to the incidence of Noma. Infections and malnutrition impair the immune system, and this is central to pathogenesis for the occurrence of Noma. Acute necrotising gingivitis and oral herpetic ulcers are possible antecedent lesions, and infection by a number of micro-organisms can cause a rapid progression to Noma.

Noma is called 'the face of poverty' because factors associated with poverty—chronic malnutrition, poor oral hygiene, poor sanitation, exposure to human and animal faecal matter and recurrent bacterial or viral infections—all contribute to the progression of Noma. According to WHO figures, one half of the Indian population defaecates in the open, causing major contamination of water sources leading to many infectious illnesses, especially diarrhoeal disease. The repeated episodes of diarrhoea, in turn, are a major source of chronic malnutrition. All these factors lead to decreased immunity, and recurrent bacterial and viral infections. Noma can progress easily in such populations, as seen in the Sub-Saharan Noma belt.

Role of malnutrition in pathogenesis of Noma

Malnutrition is defined as excess and deficiency of energy, protein and other nutrients, leading to adverse effects on health. It is a leading world health problem, contributing especially to childhood mortality. It may present as low height for age (stunting), low weight for age (undernutrition) and low weight for height (stunting). Maternal and childhood malnutrition, especially, leads to propagation of health problems in future generation and a vicious cycle of disease, malnutrition and premature deaths. Malnutrition as such is both an outcome and risk factor for disease, and associated morbidity and mortality. The United Nations MDG 2014 report estimates that one out of every four children suffers from some form of chronic malnutrition worldwide.

Malnutrition is often described as India's silent emergency. According to UNICEF 2013 data, approximately 48% of Indian children suffer from chronic malnutrition across all income groups.

According to the world bank, the rate of malnutrition among India's children is twice that of Sub-Saharan Africa. Nearly half, approximately 60 million, of the children in India are underweight, about 45% are stunted, 20% are wasted and 75% are anaemic. Malnutrition puts a big burden on the economy of a resource limited country such as India, affecting children's chances of survival and increased susceptibility to illness, and

makes them less productive in later life. Much of this undernourishment happens during pregnancy and in the first 2 years of life. This has an irreversible negative impact on health, education and economic productivity of the country.

Association of Noma with malignancy

Acute leukaemia is the most common malignancy of childhood, and coincides with the peak incidence of Noma. So, acute leukaemia predisposing to Noma is not surprising, but Noma at presentation of acute leukaemia is rare. Noma, besides being associated with extreme poverty, results due to extreme immunosuppression secondary to debilitating illnesses. The pathogenesis is supposed to involve malnutrition, immune dysfunctions and increased susceptibility to infections.² It is heralded by impaired cell-mediated immunity and qualitative defect of neutrophils, which leads to opportunistic infection and multiplication of pathogenic bacteria and viruses with release of inflammatory mediators.⁵

Our patient was a previously well, 2½ year-old boy presenting with gangrenous stomatitis and cytopaenias. Noma has been reported with haematological malignancies^{6–10} (table 1), though most cases have been in adults.

Leukaemia has been reported to be associated with Noma only during periods of immunosuppression after intensive chemotherapy. But our patient developed Noma at the onset of disease prior to receiving any chemotherapy. This could be explained by the fact that leukaemia affects the immune system in many ways, involving the humoral, cell mediated and complement systems. T-cells in ALL were found to not express CD40 ligand and CD25. Their apoptosis rate also increases with a lack of expression of B7-1 and other activation molecules in blasts of ALL. This leads to dysfunction of T-cell proliferative and cytotoxic activity.¹¹

Historically, *Fusobacterium necrophorum* has been considered the offending microbe triggering Noma,⁵ but many a time the cultured flora is polymicrobial, especially in cases associated with malignancy.^{6–10} We documented *Enterococcus* spp as the possible offending agent, and this organism is reported to be associated with Noma.^{8–10}

Outcome of Noma

The dramatic improvement in survival rates of Noma is attributed to use of antibiotics, therefore, control of infection with antibiotics and wound care are recommended initial approaches in the management of such lesions.^{2–12} In our patient, antibiotics were able to control the infection even when the predisposing acute leukaemia remained undiagnosed and untreated. Most common Noma sequelae described are unilateral loss of the whole cheek, maxilla, palate and malar bone.¹³ The same sequelae was seen in our patient. The severe bone and soft

Table 1 Published cases of Noma associated with malignancy

Case	Author, year	Age/sex of patients	Underlying malignancy	Isolated microbial agent
1.	Weinstein <i>et al</i> , ⁶ 1974	27/F	Acute myeloblastic leukaemia	Streptococci, <i>Neisseria catarrhalis</i> , <i>Proteus</i> spp
2.	Limongelli <i>et al</i> , ⁷ 1976	63/M	Chronic lymphocytic leukaemia	<i>Bacteroides melaninogenicus</i>
3.	Bendl <i>et al</i> , ⁸ 1983	54/M	Lymphoma	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> <i>Enterococcus</i>
4.	Bendl <i>et al</i> , ⁹ 1983	60/F	Chronic myeloid leukaemia	<i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Candida albicans</i>
5.	Brady west <i>et al</i> , ⁹ 1998	30/F	T cell ALL	<i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Klebsiella pneumonia</i>
6.	Santos <i>et al</i> , ¹⁰ 2011	17/M	Acute promyelocytic leukaemia	<i>Enterococcus</i> , <i>S. aureus</i> , <i>C. albicans</i>

tissue loss secondary to Noma affects both aesthetics and function. The complex nature of the defect requires reconstructive surgery in a staged fashion with the functional aspect taking priority over the aesthetic outcome. In spite of years of experience with this illness, a well-recognised surgical approach for reconstruction of Noma sequelae still remains elusive.

CONCLUSION

In our case the diagnosis of ALL was delayed for 6 months after the onset of symptoms and by 4 months after the onset of Noma, probably because of the rarity of Noma being the presenting feature of leukaemia. The Indian subcontinent has a high incidence of malnutrition and we should consider ourselves fortunate in not encountering more of this dreaded disease. This case is a reminder that Noma is lurking in our surroundings and, with a suitable ally, such as malignancy, can cause the devastation it is infamous for. The case also highlights the need for a meticulous search for underlying illness when an unusual disease such as Noma presents in a well-thriving child. There is a need to keep up epidemiological surveillance of Noma in the Indian subcontinent, where the majority of the population is still fighting poverty and malnutrition, with high prevalence of infectious diseases.

Learning points

- ▶ Unusual infections should lead to a meticulous search for the predisposing illness.
- ▶ Debilitating illnesses can predispose to Noma even in the absence of malnutrition.
- ▶ Leukaemias can predispose to opportunistic infections, even before chemotherapy is instituted.
- ▶ Epidemiological surveillance of Noma is required in the Indian subcontinent, where the majority of the population is undernourished.

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Contributors I qualify for authorship based on making substantial contributions to the intellectual content, conception and design, and acquisition of data. Furthermore, I have participated in drafting the manuscript and critical revision of the manuscript for important intellectual content.

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