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Multi-disciplinary management of neonatal acute osteomyelitis of jaws: A report of 2 cases

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ABSTRACT

Background: Early diagnosis of neonatal osteomyelitis is often challenging due to the rarity of such cases and here we are presenting 2 case reports to add to the existing deficient literature. **Case 1**: A 15-day-old male infant presented with swelling and pus discharge from the anterior region of the mandible. Repeated culture and sensitivity tests revealed a transition from disseminated methicillin-sensitive S. aureus sepsis to methicillin-resistant sepsis. Moreover, there was swelling of the left elbow and right thigh. The Clinical diagnosis made was acute osteomyelitis of mandible associated with disseminated neonatal sepsis (LONS). A multidisciplinary approach was taken for the management by surgical debridement of the lesion alongwith removal of associated primary tooth buds, under specific antibiotic coverage. **Case 2**: A 20-day old male infant reported with pus discharge from upper lateral region of mouth past 10days. Personal history revealed, abscess in mother's right breast. A soft fluctuant pus pocket with draining sinus was present w.r.t.alveolar region of 54. CT revealed an osteolytic lesion of labial cortex of alveolar ridge in maxillary right first molar region. Pus specimen culture and sensitivity revealed growth of Staphylococcus aureus (MSSA). The clinical diagnosis of acute osteomyelitis of maxillawas made. Initially, antibiotics were prescribed which did not help and finally, surgical debridement accompanied by extraction of 54 tooth bud was done.
Conclusion: Acute osteomyelitis should always be considered as one of the differentials in infants with clinical signs of sepsis and Multidisciplinary management should be assured for the successful management of such cases.

1. Introduction

Infection of the dental follicle of theprimary tooth in neonates is an extremely rare event. This may happen owing to infantile maxillar-yormandibular osteomyelitis,or vice versa. The condition was first described by Rees in 1847, and most of the cases occurred during thepre-antibiotic era. With the advent of antibiotics, infantile osteomyelitis of maxillaand mandible, subperiosteal orbital abscesses have become rare clinical entities. However, they may occur in neglected or, more commonly, untreated patients.In pediatric age groups, the incidence of osteomyelitisis 1:5000,whereasin neonates, the incidence ranges from 1 to 3 cases for every 1000 hospital admissions.[1,2] Acute osteomyelitis, although a rare complication in neonates, is a diagnostic and therapeutic challenge. Due to their immature immunesystem, neonates are susceptibleto osteomyelitisfromexposure to infectious conditions. Preterm infants are at a higher risk for osteomyelitis because of frequent blood draws, invasive monitoringprocedures, and intravenous drug administration.[3,4] Neonatal sepsis, at present, is one of the major global public healthproblemscontributing substantially to neonatal osteomyelitis, with anestimated incidence of 1–7 per 1000 hospital admissionsand much higher morbidity and mortality rates.[5,6] A slight male predilectionwas seen (Male: Female, 1.6:1.) with preterm infants at higher risk.[1,7,8] Based on the age of onset, neonatal sepsis is of two types; early-onset neonatal sepsis (EONS; occurring during pregnancy most commonly due to infection from the maternal genital tract) and Late-onset neonatal sepsis (LONS; occurring within 72 h postnatally due to nosocomial natureof the community environment).[9] Osteomyelitis and septic arthritis in preterm infants are mostly due to clinical procedures like, invasive procedures, intravenous or intra-arterial catheters, parenteral nutrition, ventilatory support, and bacteremia with nosocomial pathogens.[10,11] Ju KL. (2011) in a retrospective, reported 129 cases of osteomyelitis in children but, the average age of patients was 11years (ranges from 1 to 18years).[12] Early diagnosis of neonatal osteomyelitis is difficult because of the paucity of clinical signs and

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symptoms, butithas to be included in the differential diagnosis when late-onset or prolonged neonatal sepsis is present, as theoutcome is dependent on rapid diagnosis and theimmediate start of treatment. The literature is deficient in early detection and management of cases of acute osteomyelitis of thejaws in infants. The current cases presenting multi-disciplinary management ofacute osteomyelitis of the right body of themandible associatedwith disseminated S. aureus sepsis and isolatedacute osteomyelitis of the right maxillary alveolus in relation to the first primary molar tooth bud.

2. Case 1

A 15-day-old male infant reported to our Pediatric and preventive dentistry departmentwith the complaint of pus discharge fromlower anterior tooth regionfor past 4 days. Antenatal history revealed that the baby was born to anon-consanguineous married healthy couple by normal vaginal delivery 2 weeks earlier,and lower segment caesarean section (LSCS) phototherapy was given for 12 h and discharged uneventfully on day 4.

On the 7th day of discharge,he presented with the symptoms of fever (102°–103 °F), reduced intake of feed, limited movement,and swellingofthe left elbow, which was insidious in onset and progressive in natureforwhich medical consultation was taken.On day 15,thepatient reported to Pediatric Centre with chief compliant ofulceration, pus discharge in mandibular anterior region,and swelling in the left elbow joint region. The bloodsample was sent for culture and sensitivity and it was found sterile. From the above finding, this was suspected to be a case of Pelvic inflammatory disease/Late-Onset Neonatal Sepsis (LONS), and intravenous cloxacillin (50 mg/kg, Q6H) was started,and the patient wasreferred to theunit of Pediatric and preventive dentistry for further evaluationand management.

On extraoral examination, diffuse swelling on therightside of body of the mandiblewas presentwithout any change in colororluster of theskin. However, on palpation, there wasa local rise intemperatureand swelling wassoft in consistencywith ill-defined borderswithout appreciable pulsations. On intraoral examination, an ulceration (2 × 2 mm) with asinus opening was present in the midline over the labial aspect of the mandibular alveolar ridge.On palpation, rightmandibular body region was tender, associated with copious amount of creamy white viscous pus discharge through the sinus opening (Fig. 1).An intraoral periapical radiograph was taken, which did not show any sign of pathology(Fig. 2). Intraoral pusdischarge was collected and sent for culture and sensitivity and the result revealedmethicillinsensitive staphylococcus aureusinfection. Repeated culture and sensitivityafter 1weekshowedmethicillin resistant staphylococcus aureus (MRSA) sensitive to linezolid, teicoplanin, vancomycin, and doxycycline (Table 1).Blood cell investigation revealed a raised total leukocyte count (TLC (x 10^3/L) = 22.38), erythrocyte sedimentation rate (ESR = 6 mm), and immature granulocytes(1.4 %)(Table 2).Biochemical investigationsshowa tremendous increase inC-reactive protein (CRP) (54 mg/L, normal range 0.5–3.5 mg/L) (Table 3.) and immunologic investigations show amarked increase in IgM levels (62 mg/dl), with a slight reduction in IgG levels (Table 4). Based on the above investigations, a blood sample was sent for genetic testing (whole exome sequencing)and it was found that the JAK3 and NFE2L2 genes were affected, representing severe a combined immunodeficiency of unknown significance(Fig. 3).During this time period of 1 week, even after IV antibiotic administration, swelling appearson

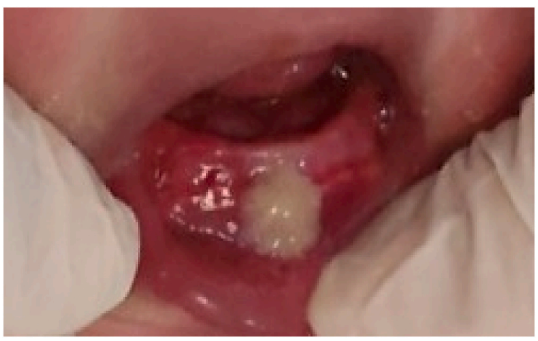

Fig. 1. Ulceration in the mandibular alveolar crest on labial surface associated with copious creamy white pus discharge on palpation, representing sinus formation.

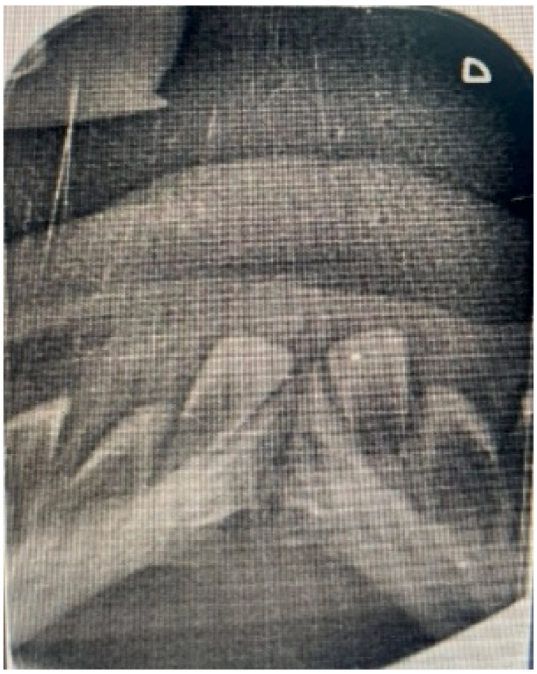

Fig. 2. Intra-oral periapical radiograph of mandibular anterior region, which didn't show any pathologic sign.

Table 1
Represents reports of Culture and sensitivity tests of both of the cases (MSSA; methicillin sensitive staphylococcus aureus, MRSA; methicillin resistant staphylococcus aureus).

	Case 1		Case 2
	Initial	After 1 week	Initial
Blood Culture	Sterile	Sterile	Sterile
Pus Culture from mouth	MSSA	MRSA	MSSA

Table 2
Represents blood investigations reports of both of the cases of acute osteomyelitis.

	Result Case 1	Results Case 2	Reference Range
Haemoglobin (gm/dL)	13.8	11.2	13.5–21.5
Platelet count (x 103/L)	445	345	210–500
TLC (x 103/L)	22.38	23	5–21
ESR (mm in 1st hr)	6 mm	5 mm	0–4
Immature Granulocytes (%)	1.4	NA	0–0.6

Table 3
Represents Biochemical test reports of both of the cases of acute osteomyelitis.

	case 1	case 2	Reference range
Creatinine (mg/dL)	0.18	0.45	0.5–1.2
Protein total (g/dL)	6.4	6.7	6.4–8.3
Uric Acid (mg/dL)	2.1	3.03	3.4–7.0
CRP (mg/dL)	54	45	0.5–3.5

Table 4
Represents Immunologic test reports of changes in levels of immunoglobulins in both of the cases.

	Case 1	Case 2	Reference range
IgG (mg/dL)	572	1021	636–1606
IgA (mg/dL)	26	13	1.4–3.6
IgM	62	39	6.3–25

the right thigh region.The various differentials made were acute osteomyelitis of the mandible associated with late-onset neonatal sepsis, submasseteric abscess tuberculous osteomyelitis andparulis. Based on the above investigations and clinical correlation, acute osteomyelitis of mandible associated with disseminated late-onset neonatal sepsis (LONS) was the clinical diagnosis. Patient was planned for emergency-surgical debridement of the lesion in the mandible under GA in collaboration with the pediatric orthopedic departmentfor surgical management of abscess in right thigh, under antibiotic coverage {Meropenem (20 mg/kg, Q8H) and Vancomycin (15 mg/kg, Q8H)}. After patient preparation and nasal intubation, a crestal incision was made from mandibular midline to the right retromolar region, a subperiostealflap was raised(Fig. 4), and debridement of necrotic bone along with the removal of dental follicles in the infected area was done, followed by irrigation and suturing.Histopathological examination revealed necrotic bony fragments, inflammatory granulation tissue,and a collection of neutrophils without any evidence of neoplastic pathologythat gives a definitive diagnosis of acute osteomyelitis. Antibiotics were continued for 2weeks after the surgery. The patient was kept on close follow up for18 months, and there was uneventful healing of lesion with no signs of recurrence of infection, overall health in general and oralhealth in particular improved(Fig. 5).

3. Case 2

A 20 days old male child reportedto our department of Pediatric and preventive dentistry with pus discharge from upper lateral region of mouth since 10days which wasassociated with fever. Child was afull term and born to non-consanguineous married healthy coupleand the type of delivery wasC-section. Patients mother denied of any surgery, trauma or presence of any systemic condition. Abscess in nipple of mother's right breast was detected on the 3rd day of life and child was subsequently fed from other side. On 10th day child had fever and intraoral pus discharge from the upper right side of buccal gingiva in primary first molarregion. On clinical examination, no extra oral finding was seen and intra-orally soft fluctuant pus pocket with draining sinus was present w.r.t alveolar region of 54(Fig. 6). Computed tomography (CT) was done under sedation that shows osteolytic lesion of labial cortex of alveolar ridge in maxillary right first molar region as shown in Fig. 7. Based on clinical and radiographic findings, various differential diagnosis taken into consideration were Acute Osteomyelitis, Focal inflammatory lesion, infected tooth bud, Tubercular osteomyelitis, Fungal infection. Pus sample collected from the intra-oral sinus opening was sent for culture and sensitivity which showed growth of Staphylococcus aureus (MSSA)(Table 1). Blood reports showedquantitative rise in CRP (45 mg/L, normal range 0.5–3.5 mg/L), raised TLC (TLC (x 10^3/L = 23; normal = 5–21) slightly increase in ESR(ESR = 5 mm in 1st hr; normal range 0–4 mm in 1st hour)(Table 2 and 3)andimmunologic investigations show marked increase in IgM levels (39 mg/dl)(Table 4). Intravenous ciprofloxacin (10 mg/kg/12 hourly) and Amikacin(10 mg/kg/12hourly) was started as per the sensitivity reports for 14 days. No resolution of pus discharge was seen after 14days of intravenous antibiotic exposure. Surgical exploration was planned and patient was taken under general anesthesia after pre-anesthesia clearance under the antibiotic coverage, crestal incision was given and infected maxillary right first primary molar tooth bud was removed along with the surrounding granulation tissue(Fig. 8).Peripheral ostectomy and debridement of surrounding bone was done with curate followed by normal saline irrigation and suturing. Patient was discharged after 24 h and post-surgery I.V amoxycillin clavulanic acid (40 mg/kg/12hourly) was

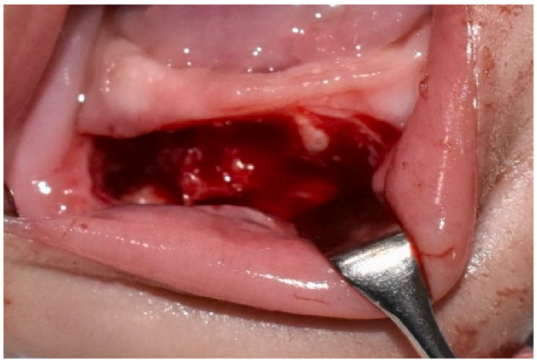

Fig. 4. Shows a crestal incision given on right quadrant of mandibular, subperiosteal flap raised followed by extraction of toot buds (85–81).

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
JAK3 **(-)** (ENST00000458235.7)	Exon 6	c.571A>G **(p.Lys191Glu)**	Heterozygous	T cell-negative (T-), B cell-positive (B+), natural killer cell-negative (NK-) severe combined immunodeficiency (OMIM#600802)	Autosomal recessive	Uncertain Significance
NFE2L2 **(-)** (ENST00000397062.8)	Exon 5	c.929C>G **(p.Ser310Cys)**	Heterozygous	Immunodeficiency, developmental delay, and hypohomocysteinemia (OMIM#617744)	Autosomal dominant	Uncertain Significance

Fig. 3. Represents genetic testing of case 1, which shows JAK3 and NFE2L2 genes were affected representing severe combined immunodeficiency of unknown significance.

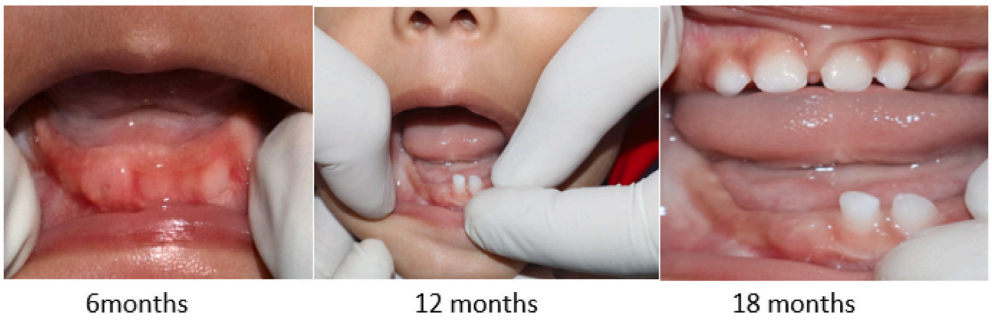

Fig. 5. Represents uneventful healing of lesion and eruption of primary dentition at follow-up of 6months, 12 months, and 18 months of case 1.

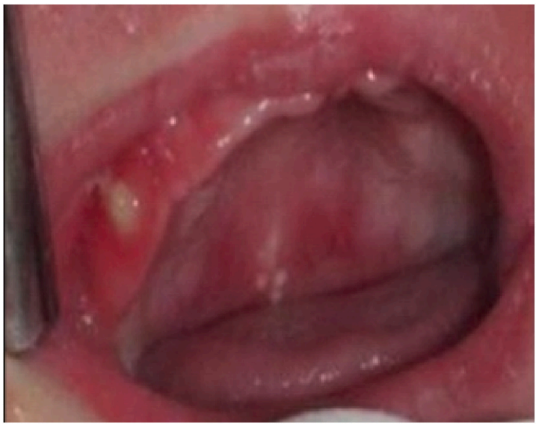

Fig. 6. Ulceration and creamy white pus discharge from sinus in the maxillary alveolar crest on labial surface in region of 54.

administered for 1 week. Histopathological reports showed inflammatory granulation tissue comprised of proliferated blood vessels, polymorphs and lymphocytes along with bony fragments and foreign materials suggesting acute osteomyelitis of maxillary alveolar bone (Fig. 9). Clinical symptoms were reduced within 24 h without any spike in fever, child was shifted to breast feed after 24 h. Further,CRP levels were continuously monitored andit was observed that they reduced sequentially to normal level(1.5 mg/L). After 20 months of close follow-up patient was well enough without any sign and symptoms of recurrent infection with improved oraland general health(Fig. 10).

4. Discussion

Neonatal sepsis has been reported as asignificant risk of morbidity and mortality, with 15 % of neonatal deaths worldwide andthehighest incidence of clinical sepsis (17,000/1,00,000 live births), and the case fatality rate ranges between 25 % and 65 %.[13,14] Initially, the clinical signs and symptoms are nonspecific and mild, including temperature instability and feeding intolerance.[15] As the disease progresses, more specific signs maybe present, such asdisability, local swellings, or erythema.[16] Due to the presence of these nonspecific symptoms, patientsshould be kept on empirical antibiotics. Apart from immaturity, other well-recorded risk factors for neonatal sepsis include the long-term use of invasive interventions, such as mechanical ventilation and intravascular catheterization, the failure of early enteral feeding with breast milk, prolonged duration of parenteral nutrition, hospitalization, surgery, and underlying respiratory and cardiovascular diseases.[17,18] The manifestations of typical acute osteomyelitis include redness or swelling at local sites, limited activity,and fever, as seen in both of our cases. Acute osteomyelitis of the mandible resulting from MRSA infections, as seen in our case1and few cases are reported in literature,[19,20] and in case2, MSSA infection of the maxilla was found, which is more frequently reported.A unique finding in our first case report was that blood cultures were sterile and pus cultures showed a transition from MSSA to MRSA(Table 1). Early diagnosis of neonatal osteomyelitis is often challenging, as radiography may not be helpful since destructive bone changes do not appear until 7–14 days of disease. Laboratory findings frequently show normal leukocytic count, ESR, and elevated CRP in the first few days, as reported in the present cases. However, computed tomography and MRI are considered for the assessment of osteolytic changes in bones and theinvolvement of adjacent vital structures. In addition to the pus culture and sensitivity, blood investigations like TLC count and CRP levels help in the early diagnosis of such conditions. According to Paakkonen M[21], the hypersensitive CRP (hs-CRP) level is a monitoring index for the course of disease,and the termination of antibiotics is considered when its levels are $\leq$20 mg/L. According to Ju KL[22], four of these variables were independent predictors of MRSA infection, including temperature ($p < 0.001$), hematocrit value ($p = 0.003$), white blood-cell count ($p < 0.001$), and C-reactive protein level ($p < 0.001$), and in both of thepresent cases,all four variables were raised. In addition to the hematological investigations, culture and sensitivity as well asimmunological and

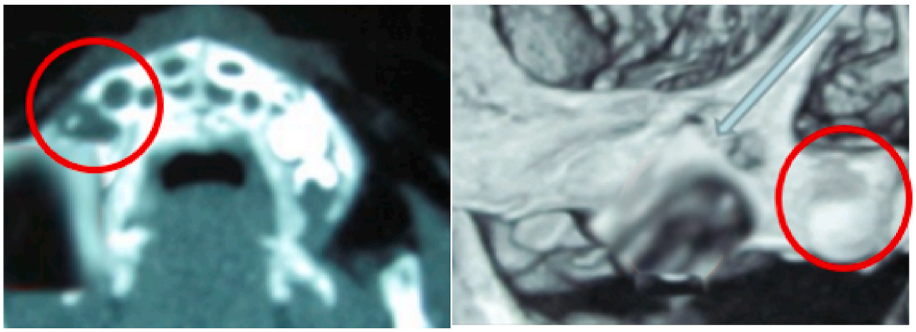

Fig. 7. Represents computed tomography of case 2 which revealed osteolytic lesions and radiolucency in relation to 54 with break in continuity of buccal aspect of alveolar bone.

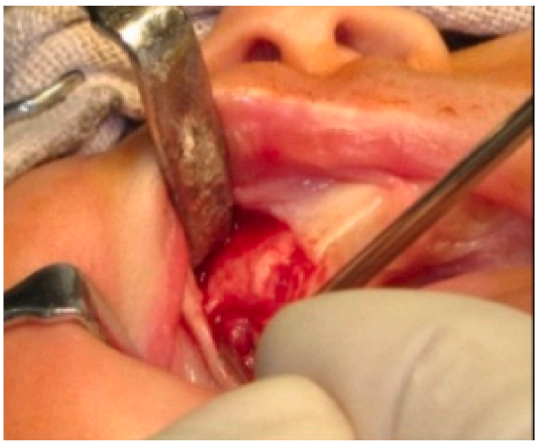

Fig. 8. Represents a crestal incision given from 53 to 55 tooth region, subperiosteal flap raised followed by extraction of 54, curettage, and debridement.

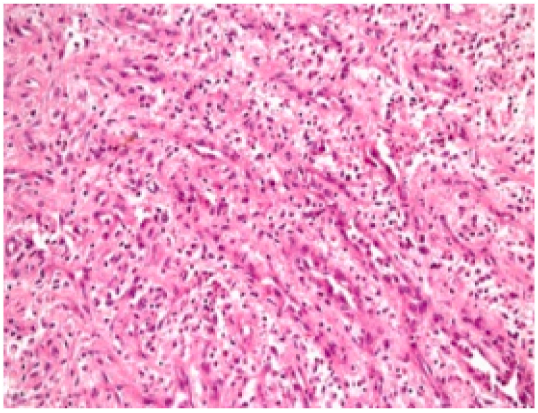

Fig. 9. Histological study of the osteogenic tissue inflammatory granulation tissue comprised of proliferated blood vessels, polymorphs and lymphocytes along with bony fragments and foreign materials suggesting acute osteomyelitis of maxillary alveolar bone (HE, x400).

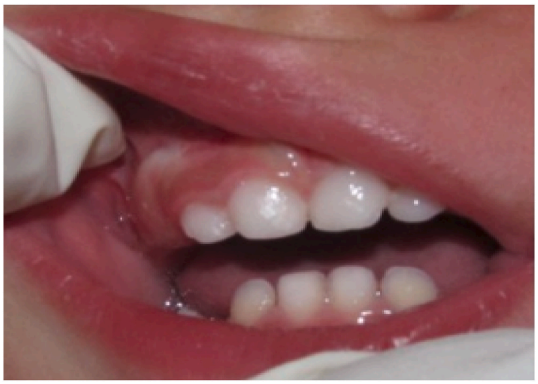

Fig. 10. Represents uneventful healing of lesion and eruption of primary dentition at follow-up of 20months.

genetic testing were done in the present case1to rule out any significant immunological deficiency. On confirmation of the diagnosis of osteomyelitis, antimicrobial therapy should be administered against the most common bacterial isolates responsible, depending on the age group. In infants, the predominant pathogen is Staphylococcus species[22] hence, it is recommended to begin a regimen that includes anti-staphylococcal agents[23]. For neonates and infants at risk for hospital-acquiredinfection (methicillin-resistant S. aureus [MRSA]), vancomycin instead of amoxicillin should be preferred.However, in our case 1, there was a transition from methicillin sensitive S. aureus to methicillin resistant S. aureus antibiotic regimen was changed with the change in sensitivity to drugs.Intravenous drug administration is recommended for 2–3 weeks, followed by oral medication[Kiechl-Kohlendorfer U; 2013]. Delay in therapy, and presence of MRSA infection increase the risk for complications, including pathologic fracturesandtemporomandibular joint disorders, and if systemic complications persist, it leads to death[24]. In the present cases, after culture and sensitivity, i.v antibiotics were started,and aggressive surgical debridement of jaw bones was done along with the removal of infected dental follicles.Orthopedic surgical debridement of right thigh was done in case 1, followed by 2 weeks post-surgery antibiotic coverage. After a follow-up of 18months patients general as well as oral health was significantly improved.C. Zhan et al. (2019)[25] reported 17 cases of infant osteomyelitis, among them, in 2 cases, the maxilla was affected. Thecomparison of demographics, location, signs, investigations, and management of those 2 cases with our 2 cases is shown in Table 5. Also[26], reported one case of osteomyelitis of maxilla in infants; however, the details regarding the signs and symptoms, investigations were not available, but similar to our cases, surgical management under antibiotic coverage was rendered to the infant. So, for the early, accurate diagnosis and management of acute osteomyelitis in infants' multidisciplinary approach, proper investigations that encompasses culture and sensitivity, blood cell count, especially TLC, CRP levels, ESR values, and immunological investigations are of utmost importance. In addition to the above-mentioned investigations, whole gene sequencing was done in our first case report, which shows an immunological deficiency that has yet to be reported in the literature.Owing to the limited immunological compentency of neonates, a rapid spread of osteomyelitis in jaw bones might occur.A multidisciplinary and surgical approach at the early stages of osteomyelitic lesions prevented complicated bone destruction of the mandibleand prevented serious complications like the spread of infection to the orbit, cranial cavity, or nasal cavity, which could have led to life threatening conditions.So, prompt delivery of care will improve the prognosis and limit its further spread.

5. Conclusions

- Neonatal acute osteomyelitis is a rare complication that offers a diagnostic and therapeutic challenge.
- Acuteosteomyelitis should always be considered as one of the differentials in infants with clinical signs of sepsis, but with no obvious focus, to facilitate early diagnosis and theinitiation of appropriate therapy.
- Multidisciplinary management should be assured for the successful management of such cases of osteomyelitis associated with immunodeficiency.
- Acute osteomyelitis can't be ruled out with a single test; a combination of a vigilanthistory, clinical examination, imaging, laboratory tests (especially CRP, Ig levels, and hemocrit values), and aspiration or biopsy are required to make anearlydefinitive diagnosis and an accurate treatment plan.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the formin whichthe patient(s) hasgiven his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and thatdue efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Table 5
Represents comparison of the recently reported cases of acute osteomyelitis with the present case reports.

Details	C. Zhan et al., 2019 (Out Of 17 Cases only 2 were in jaws)			Our Cases	
	Case 1		Case 2	Case 1	Case 2
Age/gender	17 Days Male		26 Days Male	15 days Male	20 days Male
Location	Right side of Maxilla		Right side of Maxilla	Right side body of the mandible	Right side of maxilla
Signs	soft tissue swelling right mid face region		Swelling of right eyelid	diffuse swelling, local rise of temperature, creamy white viscous pus discharge through the sinus	Fluctuant pus pocket with draining sinus
Investigations	Radiographic	CT: bone destruction in the right maxilla. MRI: soft tissues welling, sub-cutaneous nodular abnormal signal in right face	CT: soft tissues welling of the right eyelid.	Intra-oral periapical radiograph does not reveal any significant finding	CT: osteolytic lesion of labial cortex of alveolar ridge in maxillary right first molar region
	Culture Sensitivity	Blood and Pus shows MRSA	Blood and Pus shows MSSA	Blood and Pus initially shows MSSA and repeated culture and sensitivity showed transition to MRSA	Pus shows MSSA
	CRP Levels	83.33 ± 40.60 mg/L (Mean of all non-surgical cases)	74.52 ± 58.22 mg/L (Mean of all surgical cases)	54 mg/L *(IgM levels Markedly raised(*62 mg/dl), *genetic testing shows* JAK3 and NFE2L2 *genes were affected)* *TLC (x 10^3/L) = 22.38* *ESR* 6 mm	45 mg/L *TLC (x 10^3/L)* = 23 *ESR* **5 mm**
Management	Conservative	Vancomycin + Ceftriaxone sodium	Vancomycin + meropenem	Meropenem (20 mg/kg, Q8H) + Vancomycin (15 mg/kg, Q8H)	ciprofloxacin (10 mg/kg/BD) Amikacin (10 mg/kg/BD
	Surgical	No	Yes	Yes	Yes
Follow -up		Not specified	Not specified	18 months	20 months

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Ethical clearance

Patients parents were informed and allowed to review the contents and then written consent was taken from them. Editing and removal of confidential content was done and ethically cleared by the institute.

Source of funding

No source of Funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors have made substantial conceptual, design contributions or gathered and analyzed important data, and helped to draft and critically revise the paper in keeping with important intellectual content. The authors declare that they have no conflicts of interest.

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