Review Article

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Neonatal Riga-Fede disease: A systematic review of 84 cases collected over 120 years

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TUGSE,
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ABSTRACT

Background: Traumatic ulceration of the tongue due to congenital teeth is known as Riga-Fede disease (RFD). The literature on RFD consists largely of anecdotal case reports, thereby lacking valid clinical recommendations. While managing a newborn with RFD complicated by Ludwig's angina, this knowledge gap was recognized. Therefore, this systematic review was conducted to gain insight into the optimal management and the possible complications of RFD.

Methods: A literature search was conducted using PubMed, Google Scholar, and Science Direct, supplemented with African Journals Online, Indmed, and manual searches. Papers published between 1900 and July 2023 in any language were retrieved. Neonates with natal or neonatal teeth and ulceration of the oral mucosa were included. Papers with incomplete data and review articles were excluded.

Results: A total of 84 newborns with RFD from 62 published reports (including the case reported herein) were analyzed. Most of the reports were from the Indian subcontinent, and the frequency of reporting has increased since the year 2000. Tongue ulceration in all cases was due to mandibular incisors. There was no significant difference in the median duration of healing between the tooth extraction group (14 days) and the conservative management group (18 days). There was only a very weak positive correlation between the duration of symptoms and healing time, which was statistically insignificant.

Conclusion: Healing of mucosal ulcers in RFD is often protracted and does not appear to be influenced by the duration of symptoms or by the modality of treatment. Extraction of the offending teeth is more common (75% of cases) than conservative management, such as grinding (ameloplasty) or resin capping of teeth. RFD is mostly a benign disorder; however, serious complications such as meningitis, Ludwig's angina, and soft tissue abscesses can rarely occur with Staphylococcus aureus infections.

INTRODUCTION

Riga-Fede disease (RFD) is a benign disorder of the tongue or lip in which a traumatic ulcer or granuloma is caused by repetitive friction over an erupted tooth.[1] It is also known by various synonyms such as aphtha cachexia,[2-5] Cardarelli's syndrome,[2] TUGSE (Traumatic ulcerative granuloma with stromal eosinophilia),[3] sublingual traumatic ulceration,[4,5] eosinophilic granuloma of the tongue, and sublingual granuloma of infancy.[6]

RFD can occur at any age. Dominguez-Cruz et al. classified it into 'precocious' (< 6 months of age) and 'late-onset' (> 6 months of age) types based on the timing of tooth eruption in infants.[7] In older children and adults, RFD may be associated with neurological disorders such as Riley-Day syndrome, Tourette syndrome, Lesch-Nyhan syndrome, and familial dysautonomia.[2,7] In contrast, neonatal RFD is caused by congenital (natal or neonatal) teeth in the absence of any underlying pain insensitivity syndromes. Being a painful condition, it interferes with breastfeeding. Although malnutrition and death were originally reported in the pre-antibiotics era (hence the name aphtha cachexia), such serious complications of RFD are now extremely rare.

Recently, we treated a newborn with life-threatening Ludwig's angina that complicated RFD. While searching for therapeutic guidance, we noticed that the literature on RFD is predominantly restricted to either single case reports or short series, thereby

lacking any meaningful clinical recommendations. This deficiency prompted us to undertake a systematic review of published case reports. This review is aimed to identify the effect of various treatments on the healing time of mucosal ulcers and to identify the potential complications of RFD.

METHODS

Description of the index case

A 12-day-old full-term female newborn, weighing 2200 grams (birth weight 2300 grams), was admitted with a bleeding tongue ulcer that had developed over a few hours. She was born with a congenital left central mandibular incisor tooth (Tooth number 71; FDI World Dental Federation notation), which caused difficulty in breastfeeding. On the fourth day of life, the tooth partially broke when her grandmother attempted to remove it at home. Within a day, she developed an ulcer on the adjoining area of the tongue due to friction against the broken tooth. On the eighth day of life, she developed swelling on the left side of her face and neck, intermittent oozing of blood from the ulcer, fever, and refusal to feed. Her parents had tried unspecified native medicine.

Figure 1: Clinical photographs of the index case. (a) Intraoral view showing retained tooth (arrow) and bleeding ulcer; (b) Extra-oral view showing submandibular cellulitis with ecchymosis

Clinical examination revealed an actively bleeding ulcer on the ventral surface and tip of the tongue, extending to the alveolar ridge and lower lip. The base of the ulcer was indurated, painful, and covered with black slough. A broken remnant of the tooth with a sharp edge was also noticed (Fig. 1a). The left side of the neck and submandibular area were swollen, warm, tender, red, and ecchymotic, consistent with spreading cellulitis (Ludwig's angina) (Fig. 1b). Breathing difficulty and tongue edema were absent. She was diagnosed with Ludwig's angina complicating Riga-Fede disease (RFD).

Active bleeding was controlled with local pressure for 10 minutes. She was given intravenous empirical antibiotics (meropenem, vancomycin, and metronidazole), a vitamin K injection, and a whole blood transfusion. Feeding was resumed through a nasogastric tube. A brief course of intravenous dexamethasone was given for 3 days to prevent airway edema.

Ultrasonography of the neck revealed soft tissue edema with multiple pockets of pus collections. Blood and wound cultures grew methicillin-resistant Staphylococcus aureus (MRSA) that was sensitive to vancomycin, amikacin, and linezolid. Empirically started antibiotics were revised accordingly to vancomycin alone. Hemoglobin was 12.6 g/dL, leukocyte count was 27,100/mm^3, platelet count was 22,000/mm^3, C-reactive protein was 9.2 mg/dL, and prothrombin time was 15.7 seconds (International Normalized Ratio 1.3). Other laboratory parameters were normal. With multiple platelet-concentrate transfusions, the platelet count improved to 158,000/mm^3 by day 3 of hospitalization.

On the fourth day of admission, she was surgically explored under general anesthesia. Extraction of the broken tooth remnant, drainage of cervical abscesses, and debridement of the sloughed-out ulcer base were performed. Histopathology and fungal culture of the slough were unremarkable except for the presence of acute inflammatory infiltrate.

The baby was discharged after 17 days of NICU care. At discharge, oral linezolid was prescribed for 10 days due to mild induration of soft tissue in the neck. Two weeks later, the ulcer had healed well, but she was noted to have weakness of the lower facial muscles on the left side. At a 1-year follow-up, she was found to be thriving well; however, facial asymmetry on crying persisted, suggesting either an operative injury to the mandibular branch of the left facial nerve or post-inflammatory fibrosis of the facial muscles of expression.

Literature Review – Search Strategy

Scientific articles on RFD and congenital teeth were searched using PubMed, Google Scholar, ScienceDirect, African Journals Online (AJOL), and IndMed. Since the last two sites do not have effective search logic, they were treated as supplementary data sources. Google Scholar was set to exclude citation records. The search strings used were: "Riga-Fede", "Congenital teeth/tooth", "Natal teeth/tooth", "Neonatal teeth/tooth", "Cardarelli aphthae", "Aphthae cachexia", "TUGSE", "Traumatic ulcerative granuloma with stromal eosinophilia", "Eosinophilic AND (tongue OR lingual) AND (ulcer OR granuloma)" and "(sublingual OR tongue) AND (traumatic ulcer* OR granuloma)". Searches were restricted by title words within the period 1900 to 2023 July. The age restriction was not applied to pre-screening searches. Articles published before the year 1900 were not considered mainly because of their inaccessibility. (Supplementary Table-A) Online searches were complemented with manual searches of relevant journals and cross-referencing of citations from published papers.

The following types of articles were excluded from analysis: Duplicate records, patient age beyond the neonatal period, reports with inadequate (<75%) patient details, articles without the description of new patients (eg. review articles, letters to editor, comments, and editorials) and reports of congenital teeth without oral ulcers or vice versa. Age at the onset of symptoms rather than the age at clinical presentation was used to define the inclusion criteria of 'neonatal age' (<30 days). For preterm babies, corrected gestational age was used. Case reports from gray literature, conference proceedings, university theses, and lesser-known regional journals were also included. Non-English articles were translated using Google Translate.

Details on the year of publication, country of origin, age and sex of patients, duration of symptoms, presenting features, nature of the treatment, time required for healing, and complications were entered in a Microsoft Excel spreadsheet (version 2016). As many of the publications did not contain sufficient description to differentiate 'feed refusal' from 'painful feeding', both were clubbed under 'feeding difficulty of the newborn'. However, maternal nipple soreness or pain due to natal teeth was marked separately from 'feeding difficulty'.

Statistical analysis

Statistical calculations and graphs were done using GraphPad Software© version 2023. Non-parametric tests were chosen for analysis because of the non-normal distribution of data. The correlation coefficient was calculated using Spearman rank correlation and the duration of healing between various therapy groups was compared using the Wilcoxon-Mann-Whitney U-test. Statistical significance was set at $p<0.05$

RESULTS

The PRISMA chart (Fig. 2 – supplementary file) summarizes the search results and article selection process. A total of 84 newborns with RFD from 62 published reports (including the present one) were considered for analysis. Table 1 summarizes the demography. Offending teeth had been extracted in 63 neonates (75%), while 3 were observed without any intervention. Conservative management included smoothening the sharp edge of the teeth either by grinding (n = 16) or by providing a protective tooth cap (n = 6). Often, these treatments were supplemented with topical application of triamcinolone (n = 11) to facilitate healing by reducing inflammation, or with topical benzocaine gel - Orabase™ (n= 2) to relieve pain.

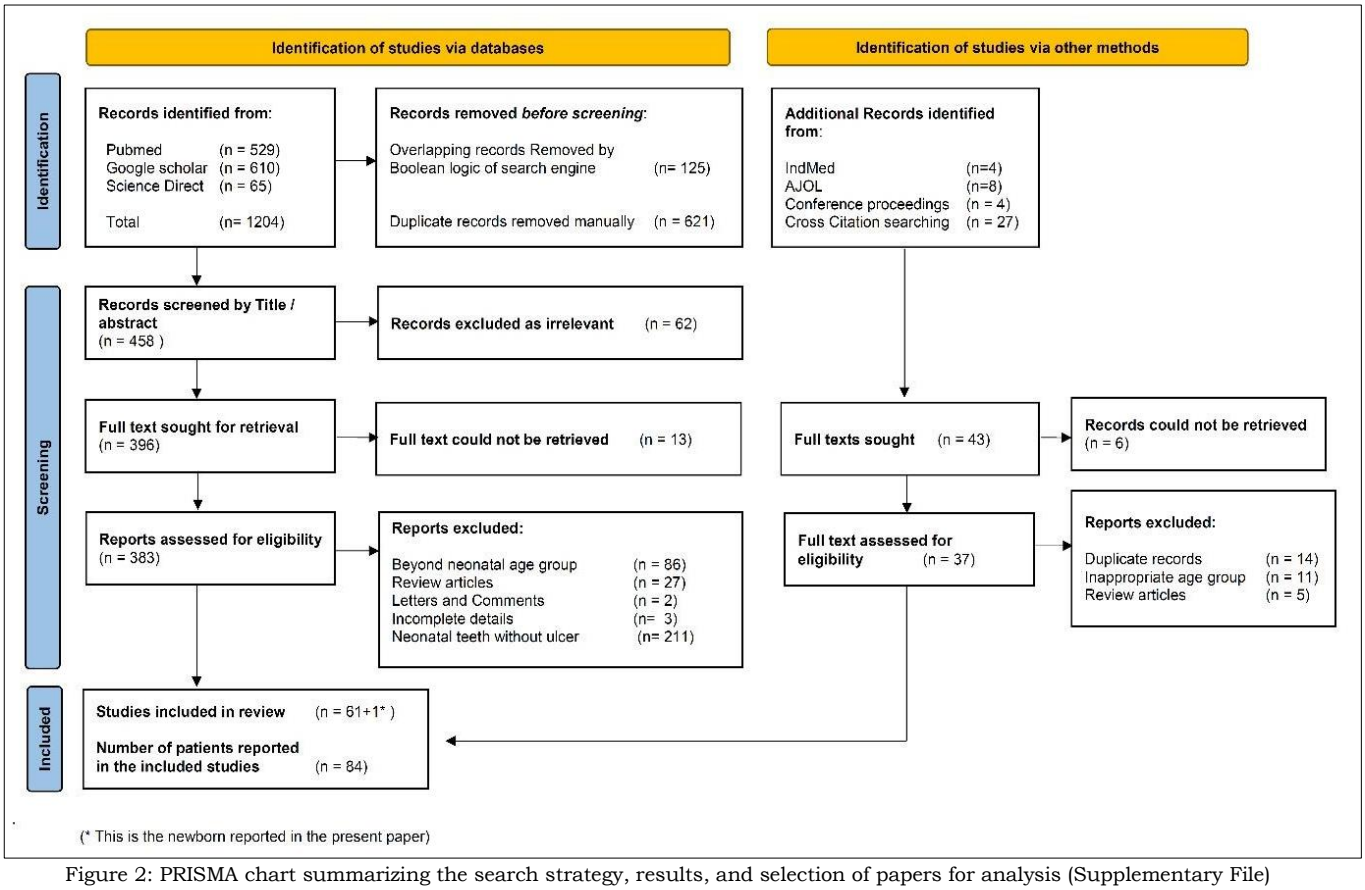

Figure 2: PRISMA chart summarizing the search strategy, results, and selection of papers for analysis (Supplementary File)

Oral ulcers healed at a median duration of 14 days (95% CI 13-21 days; range 2-90 days). There was only a very weak positive correlation between the duration of symptoms and healing time (n = 32; Spearman rs = 0.01295; p = 0.94) (Fig. 3).

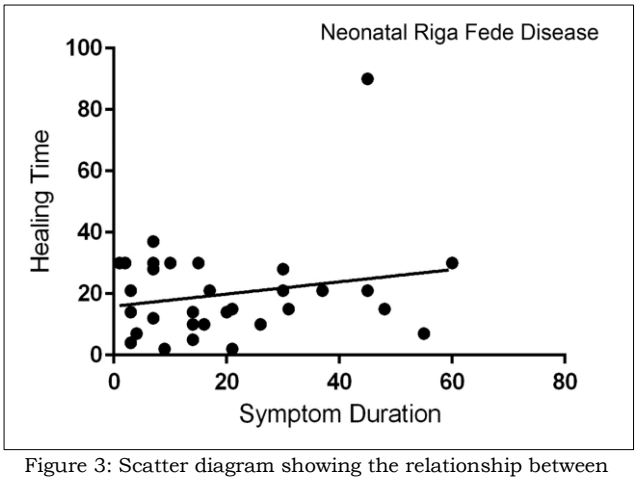

Figure 3: Scatter diagram showing the relationship between duration of symptoms (days) and healing time (days) in neonatal Riga Fede Disease.

For analyzing the therapeutic outcomes of various treatment modalities, adequate data sets were available for 48 neonates. The median duration of healing between the tooth extraction group (n= 38; Median 14 days) and the conservative management group (n=10; Median 18 days) did not differ significantly (Mann-Whitney U=493; p = 0.80).

DISCUSSION

In 1857, Urbino Cardarelli first described a peculiar condition of tongue ulceration in infants that resulted in cachexia and death [8]. In 1881, Antonio Riga suggested that it could be caused by a less virulent form of diphtheria [8]. Between 1890 and 1896, Francesco Fede established its traumatic etiology through histological studies and suggested its causal relationship with congenital teeth [8]. In the early 1980s, Elzay [3] and Tang [9] hypothesized that the lesion originates as a traumatic ulcer of the mucosa and is subsequently turned into a granulomatous mass by the host immune reaction against foreign proteins that enter through the ulcer. Elzay coined a new acronym, TUGSE, which is commonly used in older infants and adults [3]. Although the terms TUGSE and RFD have been used interchangeably in the literature, it appears inappropriate to use the term TUGSE in neonates as their immune response to foreign proteins is impaired. This is supported by the fact that only 4% of neonates presented with a granulomatous mass lesion, while all others simply had an indurated ulcer of the tongue. However, in this context, it should also be acknowledged that neonatal lesions of RFD have seldom been subjected to detailed histological or microbiological studies. In the absence of histological studies, micro-granulomas are likely to be missed. Similarly, in the absence of microbiological studies, etiological attribution will be difficult.

Table 1: Demography of Neonatal Riga Fede Disease

Age of Presentation (Median)	21 days (Range 0 - 70)	
Age at onset (Median)	7 days (Range 0 - 31)	
Duration of Symptoms (Median)	15 days (Range 0 - 60)	
Duration of healing (Median)	14 days (Range 2 - 90)	
Sex	**n**	**%**
Male	36	43%
Female	39	46%
Unspecified	9	11%
Involved teeth's		
Tooth no 71	28	33%
Tooth no 81	14	17%
Teeth no 71 & 81	32	38%
Duplex †	3	4%
Tooth no 72	1	1%
Teeth no 71,81,82	1	1%
MI otherwise unspecified	5	6%
Common symptoms		
Feeding difficulty	57	68%
Nipple sore	2	2%
Irritable Crying	12	14%
Ulcer *	38	45%
Mass lesion	3	4%
Pain	14	17%
Bleeding	5	6%
Weight loss	3	4%
Sleep Disturbance	4	5%
Dehydration	1	1%
Asymptomatic / incidental	6	7%
Location of Ulcer		
Tip / Frenular Tongue	82	98%
Lateral border of tongue	3	4%
Lips / gums	4	5%
Geographic location		
India	48	57%
South East Asia	3	4%
Europe	12	14%
Australia	1	1%
Japan	2	2%
Middle East	5	6%
South America	8	10%
North America	4	5%
Unspecified	1	1%

* Although the presence of ulcer is a diagnostic requirement of Riga-Fede Disease, they are often detected by physicians during physical examination (sign) rather than being a presenting symptom.

† Duplex – Two teeth at the same location one behind the other

§ Teeth position are as per FDI World Dental Federation notation of primary dentition: 71 – Lower left central incisor (primary); 81 – Lower right central incisor (primary); 82- Lower right lateral incisor (primary)

The chronological distribution of publications on RFD reveals a notable increase in frequency after the year 2000. Between 1903 and 1944, only 9 new cases of RFD were reported worldwide, none of which involved neonates [6]. Elzay reviewed 70 cases of RFD reported between 1903 and 1983, with only one involving a newborn [3]. We agree with Elzay's assertion that

neonatal RFD may not be as rare as perceived, and the apparent rarity is likely to be due to publication bias against case reports. The proliferation of open-access journals may have contributed to the recent increase in the reported cases of RFD. Approximately 57% of cases have been reported from India, prompting further investigation into whether this geographical disparity relates to factors such as malnutrition, tropical climate, genetic predisposition, or publication bias.

Serious complications and deaths associated with RFD were well documented in the pre-antibiotic era but have become extremely rare since then [5,8]. Picciotti et al. reported a newborn with staphylococcal meningitis complicating RFD [10]. White et al. described a neonate with a subperiosteal abscess of the orbit due to staphylococcal infection from congenital teeth, though not associated with RFD [11]. Kamboj reported a newborn with a submandibular abscess complicating natal teeth without RFD [12]. In our case, RFD was complicated by Ludwig's angina due to methicillin-resistant Staphylococcus aureus (MRSA). Dixon and Steele suggested that infantile Ludwig's angina due to MRSA may represent a distinct clinical syndrome [13]. To date, only two cases of neonatal Ludwig's angina have been reported worldwide [14,15], none of which were associated with RFD.

Ludwig's angina is a life-threatening condition characterized by spreading cellulitis of the sublingual space, which can rapidly lead to airway edema and respiratory distress. Prompt administration of antibiotics and surgical drainage of pus are crucial for a successful recovery. In older children and adults, prophylactic tracheostomy is often recommended to mitigate the risk of laryngeal edema [16,17]. In the absence of published neonatal experience, our limited encounter with a single case suggests that a short course of corticosteroids may be beneficial in reducing inflammatory edema, thereby potentially avoiding neonatal tracheostomy and its associated complications. Thus, the theoretical extrapolation of adult experience with corticosteroid usage in Ludwig's angina [16] is supported by our clinical observation in a neonate.

We have observed that the literature on RFD is filled with various dogmas and myths. Firstly, the distinction between natal teeth (present at birth) and neonatal teeth (erupting within 30 days after birth) holds no practical significance. Therefore, they can collectively be referred to as 'congenital teeth'. Secondly, there seems to be unwarranted hesitation towards dental extraction in neonates. Mucosal ulcers of RFD typically heal spontaneously once the sharp offending teeth are addressed, either through extraction or by smoothing their edges (grinding or resin capping). Concerns about extracting deciduous teeth, such as fears of adjacent teeth drifting and potential collapse of the dental arch, are often raised without clinical evidence, as seen in Gardiner's paper [18]. Despite similar healing durations between tooth extraction and conservative treatments, extraction is preferred for several reasons: (1) It is technically simpler than maintaining a resin cap or grinding a tooth in neonates; (2) Approximately 5-10% of congenital teeth are supernumerary, and up to 40% are dysplastic and mobile, making their extraction unlikely to lead to significant consequences [1]. Moreover, these are deciduous teeth that will naturally be replaced by permanent dentition over time. (3) Extraction can also alleviate maternal nipple pain and facilitate breastfeeding [19]. Therefore, we argue against the complex decision algorithms proposed by Padmanaban et al. [5], suggesting that offending teeth can be safely removed under local anesthesia. Thirdly, some authors recommend delaying tooth extraction until after 10 days of vitamin K injection to avoid hemorrhagic disease of the newborn [20]. However, this precaution may be an excessive one, given that more invasive procedures, such as repairing tracheo-esophageal fistulas, are routinely performed immediately after birth without excessive blood loss. Finally, concerns about death due to aspiration of loosened congenital teeth appear unfounded, as observed by Al-Buainain [21], who noted no documented cases of such accidents.

Prolonged healing time is a characteristic feature of neonatal RFD, with a median healing period of 14 days (range 2 – 90 days). The continuous friction of the tongue against the offending tooth may contribute to delayed ulcer healing. Interestingly, the chosen treatment modality [22] does not seem to significantly affect healing rates. Even with tooth extraction, mucosal ulcer healing remains prolonged, possibly due to tongue mobility disturbing the healing epithelium despite avoiding repetitive trauma through extraction of the congenital tooth. Notably, there are no reports of recurrent RFD, even when the offending tooth is retained.

Limitations of this review include retrospective data collection, potential publication bias against case reports, and a very small sample size within each treatment category. The number of patients reported during the pre-antibiotic era is exceedingly small, precluding meaningful comparative analyses on the influence of antibiotics on final outcomes. Notably, histological and microbiological studies of neonatal RFD are conspicuously absent in the published literature, hindering etiological attribution and the deduction of pathogenic mechanisms. Nevertheless, this report represents the first effort to consolidate

and analyze the current understanding of neonatal RFD.

CONCLUSION

Neonatal RFD may not be a rare disease but appears to be under-reported, likely due to publication bias. Extraction of the offending teeth is the most logical and straightforward treatment, although it does not necessarily shorten the healing time. The median healing time of mucosal ulcers is often prolonged, and it shows no correlation with the duration of symptoms or the treatment method (extraction versus conservative management). Tooth extraction should not be delayed or avoided out of concern for potential deformities in permanent dentition or excessive bleeding.

Although neonatal RFD is generally considered a benign disorder, potentially life-threatening complications such as meningitis, Ludwig's angina, and soft tissue abscesses can rarely occur, particularly if the ulcer becomes infected with Staphylococcus.

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REFERENCES

1. Iandolo A, Amato A, Sangiovanni G, Argentino S, Pisano M. Riga-Fede disease: A systematic review and report of two cases. Eur J Pediatr Dent. 2021;22:323-31. DOI: 10.23804/ejpd.2021.22.04.11.
2. Mohan RPS, Verma S, Gill N, Singh U, Riga-Fede disease (Cardarelli's aphthae): A report of nine cases. S Afr J Child Health. 2014;8:72-4. DOI:10.7196/SAJCH.636
3. Elzay RP. Traumatic ulcerative granuloma with stromal eosinophilia (Riga-Fede's disease and traumatic eosinophilic granuloma). Oral Surg Oral Med Oral Pathol. 1983;55:497-506. DOI: 10.1016/0030-4220(83)90236-0.
4. Goho C. Neonatal sublingual traumatic ulceration (Riga-Fede disease): reports of cases. ASDC J Dent Child. 1996;63:362-4.
5. Padmanabhan MY, Pandey RK, Aparna R, Radhakrishnan V. Neonatal sublingual traumatic ulceration - case report and review of the literature. Dent Traumatol. 2010;26:490-5. DOI: 10.1111/j.1600-9657.2010.00926.x.
6. Abramson M, Dowrie JO. Sublingual granuloma in infancy (Riga-Fede's disease). J Pediatr. 1944;24:195-8.
7. Domingues-Cruz J, Herrera A, Fernandez-Crehuet P, Garcia-Bravo B, Camacho F. Riga-Fede disease associated with post-anoxic encephalopathy and trisomy 21: a proposed classification. Pediatr Dermatol. 2007;24:663-5. DOI: 10.1111/j.1525-470.2007.00564.x.
8. Amberg S. Sublingual growth in infants. Am J Med Sci. 1903;126:257-269.
9. Tang TT, Glicklich M, Hodach AE, Oechler HW, McCreadie SR. Ulcerative eosinophilic granuloma of the tongue. A light- and electron-microscopic study. Am J Clin Pathol. 1981;75:420-5. DOI: 10.1093/ajcp/75.3.420.
10. Picciotti M, DeVice L, Viviano M, Giorgio A, Lorenzini G. Meningitis and Riga-Fede disease: an unusual condition. Eur J Pediatr Dent. 2014;15(2 Suppl):245-6.
11. White M, Harb JL, Dymerska M, Yoo SH, Eckert P, Chang D, Marston AP. Neonatal tooth infection resulting in subperiosteal orbital abscess: A case report. Int J Pediatr Otorhinolaryngol. 2021;140:110524. DOI: 10.1016/j.ijporl.2020.110524.
12. Kamboj M, Chougule RB. Neonatal tooth--how dangerous can it be? J Clin Pediatr Dent. 2009;34:59-60. DOI: 10.17796/jcpd.34.1.27h00760t6271785.
13. Dixon EE, Steele RW. Ludwig angina caused by MRSA: A new syndrome. Clin Pediatr (Phila). 2016;55:316-9. DOI: 10.1177/0009922815609400.
14. Maciag M, Sediva I, Alexander-Scott N. Submandibular swelling and fever following frenulectomy in a 13-day-old infant. Clin Pediatr (Phila). 2016;55:990-2. DOI: 10.1177/0009922815627014.
15. Steinhauer PF. Ludwig's angina: report of case in a 12-day-old boy. J Oral Surg. 1967;25:251-4.
16. Tami A, Othman S, Sudhakar A, McKinnon BJ. Ludwig's angina and steroid use: A narrative review. Am J Otolaryngol. 2020;41:102411. DOI:10.1016/j.amjoto.2020.102411.
17. Massler M, Savara BS. Natal and neonatal teeth; a review of 24 cases reported in the literature. J Pediatr. 1950;36:349-59. DOI: 10.1016/s0022-3476(50)80105-1.
18. Gardiner JH. Erupted teeth in the newborn. Proc R Soc Med. 1961; 54: 504-506.
19. Jamani NA, Ardini YD, Harun NA. Neonatal tooth with Riga-Fede disease affecting breastfeeding: a case report. Int Breastfeed J. 2018;13:35. DOI:10.1186/s13006-018-0176-7.
20. Zhu J, King D. Natal, and neonatal teeth. ASDC J Dent Child. 1995;62:123-8.
21. Al-Buainain FS, Adil A, Mustafa O. Natal, and Neonatal Teeth in Bahrain: A Review of 19 Cases. J Bahrain Med Soc. 2021;33:31-7.
22. Volpato LE, Simões CA, Simoes F, Nespolo PA, Borges AH. Riga-Fede Disease Associated with Natal Teeth: Two Different Approaches in the Same Case. Case Rep Dent. 2015; 2015: 234961. DOI: 10.1155/2015/234961.