Granuloma gravidarum: clinical features and management. 
Case report and review of the literature

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SUMMARY: Granuloma gravidarum: clinical features and management. Case report and review of the literature.


The aim of this manuscript is to clarify the state of art of granuloma gravidarum (GG), analyzing its peculiar clinical features, management and statistical data in term of stratification of the study population and to enlarge the series in the literature. GG is an oral mucosal inflammatory hyperplasia, which affects pregnant women as response to local irritation under the influence of sexual hormonal factors. Data were pigeonholed referring to the age of the patients, gestation trimester, time of development, lesion size and location, clinical features and manner of resolution. We analyzed 48 cases of GG diagnosed between 1980 and 2015, including our case report. The lesion occurred in pregnant women, mean age 28 years (SD± 6.45). It appeared as nodule located in the gingiva (70.83%) with mean diameter of 1.5 cm (SD±0.89). If symptoms of GG are manageable, the treatment of choice is observation and maintenance of oral hygiene. If uncontrolled bleeding and swallowing discomfort occur, excision is required and in extreme condition induction of labor should be considered.

KEY WORDS: Granuloma gravidarum - Pregnancy - Obstetric complication.

Introduction

Granuloma Gravidarum (GG) is a not frequent, peculiar, benign oral lesion since it affects up to 5% of pregnancies (1). Unfortunately, the imprecise and various names related to this clinical feature might cause confusion. GG develops more often on the maxillary gingiva and rarely on the lips and tongue (2, 3). The aforementioned condition, known as Pyogenic granuloma (PG), despite of its name, is not linked to inflammatory condition and is more comparable to an angioma rather than to granulomatos lesion since histologically is represented by blood vessels in section (4).

This so-called Pregnancy tumor is not a neoplasm whereas it is an inflammatory hyperplasia as response to local irritation, which is characterized by a polyoid lesion, sessile or pediced, with a rapid growth, erythematous or brownish, usually ulcerated and associated to spontaneous bleeding (5). This reactive lesion is classified under pregnancy-associated gingival disease.

The biological mechanisms behind the pathogenesis and remission of GG during pregnancy have been extensively studied. The violent endocrinological change of pregnancy is frequently associated with modifications in the function and structure of the skin and mucosa’s lymphatic and blood microcirculation (6). In the medical literature it is known that sex hormones have different biological and immunological effects. Yuan et al. (7) suggested that, in GG, the production of VEGF and bFGF is significantly higher than healthy gingiva and periodontium. In addition, the expression of angiostatin was considerably less in GG compared to production observed in healthy gingiva and periodontally involved gingiva. The molecular mechanism allowing the regression of GG after delivery remains unclear. It has been proposed that, in a poor environment of VEGF, Angiopoietin-2 (Ang-2) could cause the re-

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gression of blood vessels. Yuan and Lin (8) suggested that Tumor Necrosis Factor-α (TNF-α) upregulated the expression of Ang-2 in all endothelial cell types tested (Fig. 1). In fact, they noted that the protein’s levels of Ang-2 was highest in the granulomas in pregnancy, followed by those after delivery and normal gingiva. In GG, VEGF’s amount is considerable while it is almost undetectable after delivery when there are more apoptotic cells and less Ang-2 than in pregnancy; these findings suggest that VEGF alone or in combination with Ang-2 could protect microvessels from apoptosis, while Ang-2 alone would have no effect on this (9). The same oral changes that occur in pregnancy, such as the pronounced vascularity of the gingiva, hyperplastic gingivitis, and GG, are similarly founded in women taking oral contraceptives.

Some Authors (10, 11) suggested GG arises from a known stimulation or injury such as smoke, tartar, routine tooth brushing habits, that induce microtraumas to gingiva and cause hyperproliferation under the influence of sexual hormonal factors (5). Circulating levels of female sex steroid hormones, increasing during pregnancy, may raise Proventella intermedia counts, a Gram-negative obligate anaerobic pathogenic bacterium, in the subgingival biofilm, alter periodontal microbial plaque and so heighten the inflammatory response (12).

Whenever an oral lesion is discovered, it is crucial to formulate suitably, by biopsy findings, a differential diagnosis including several conditions. Granulomatous tissue, hyperplastic gingival inflammation, peripheral ossifying fibroma, hemangioma, Kaposis sarcoma, angiosarcoma, non-Hodgkin’s lymphoma, squamous-cell carcinoma and metastatic cancer are the most common diseases that resemble GG (13).

Concerning GG’s management, it is reasonable to set the treatment on the basis of the severity of the symptoms. If the lesion is small, painless, free of bleeding, clinical observation, and follow-up with stress on maintenance of good oral hygiene, is recommended. In presence of huge and highly vascularized lesion, which may impede routine brushing and create discomfort during mastication, or even bleeding lesion, it could be mandatory a surgical excision during pregnancy, in order to avoid possible transfusion. Cold-knife incision should extend down to the periosteum and the adjacent teeth should be deeply cleansed to remove the source of continuing irritation (plaque, calculus, foreign materials). CO2 lasers have also been used in surgical treatment of GG (14, 15). Powell et al. (16) reported the use of Nd:YAG laser for the excision of a lesion in a 36-weeks pregnant woman due to a lower risk of bleeding, compared with other surgical techniques. Fortunately, GG mostly regresses spontaneously but sometimes even recurs after surgery (4) or persists in puerperal period (17); in this case medical therapy, such as intralesional and systemic steroid treatment, imiquimod, alitretinoin gel, erythromycin and intralesional bleomycin, may be effective (18-21).

The aim of this manuscript is to clarify the state of art of this condition, analyzing its peculiar clinical features, management and statistical data in term of stratification of the study population and to enlarge the series of GG in the literature.

Case report

A 37-year-old caucasic primigravida woman in her 37th week of pregnancy, presented at our department with an isolated fleshy exophytic lesion on the dorsum of her tongue (Figure 1). No significant medical or drug history could be traced in her anamnesis.

Clinical examination revealed a bleeding pink nodule of 2 x 2 cm, hard in consistency, vascularized. The patient reported its tendency to gradually increase in size since 25th week of pregnancy causing discomfort during swallowing and talking. We consulted oral and maxillofacial surgeon, who identified the lingual lesion as a GG and suggested surgical excision in order to confirm diagnosis by biopsy and eliminate patient’s discomfort. Therefore, at 37 weeks and 4 days of gestation, she underwent, under local anesthesia, a cold knife excision of GG without complications. Histology confirmed the clinical suspect.

At 40 weeks and 4 days of pregnancy our patient went into labour and gave birth to a live male baby (Apgar 7/9) weighing 3,5 kg, by vacuum-assisted vaginal delivery for uterine hypokinesia and inadequate progress in labour. Her postoperative period was uneventful and she was discharged on the 2nd day. Up to now, her lingual lesion has not recurred.

Fig. 1 - Granuloma gravidarum: fleshy exophytic lesion of 2 x 2 cm on the dorsum of our patient’s tongue.
Methods

We analyze 46 cases of GG diagnosed between 1980 and 2015 including our case report. Data were pigeonholed referring to the age of the patients, gestation trimester, time of development, lesion size and location, clinical features, as well as the manner of resolution.

The data were initially evaluated by descriptive statistics. The qualitative variables were expressed as absolute and relative frequencies. The quantitative variables were described by mean and standard deviation. Comparison of the results for age groups, gestation period and lesion size was carried out by constructing contingency tables and applying the chi-square test. Due to the small sample size, the significance of the test was obtained via simulation using the Monte Carlo method. The software used was the SPSS version 19.0.

### Table 1 - Granuloma Gravidarum: Literature Review

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Granuloma gravidarum
Results

Literature revision of GG, including our case, consist in forty-eight cases. GG occurred in patients aged 19 to 44 years, with a mean of 28 years (SD± 6.45). In 54.4% of the cases, the lesion developed in the third trimester of pregnancy, in 25% in the second trimester and in 14.6% in the first trimester.

The most common location of GG was the gingiva (70.83% of the cases), with no statistically significant difference between the upper and lower region. The other affected sites were the tongue (18.75%), lip (6.25%), palate and buccal mucosa (4.16%). The lesions appeared as nodules with diameters of 0.5 to 3.5 cm with a mean of 1.5 cm (SD±0.89). The mean time of development was 150 days. An ulcerated surface was present in 31% of GG and the incidence of bleeding, spontaneous or upon touch, occurred in 54.16% of GG. Concerning treatment, 83.33% of the lesions were surgically excised. In 31.25% of the cases, the excision was performed few weeks or months after childbirth and in 52.08% of the cases, it was performed during pregnancy. After the removal of local irritants, three lesions (14.58%) had spontaneous remission, two of them during pregnancy.

There was a significant association between age and gestation period since the pregnant women up to 25 years old showed a tendency to develop GG in the first trimester of pregnancy (50%, p=0.057). The patients with ages between 26 and 35 years showed the lesion mainly in the third trimester (80% p=0.001). There was no association between the other clinical parameters evaluated. These characteristics are described in Table 1.

Discussion

With the exception of Cardoso’s review (22), this one is the only serie of cases, specifically examining the clinical features, management and statistical data of GG found in the literature. Thus, the present study aimed to retrospectively review all the existing cases, including our case of GG described in literature. In the present study, we analyze the obtained results. The pregnant women up to 25 years old showed a tendency to develop the lesion in the first trimester, but the majority of lesions occurred in the third trimester. The lesions were more prevalent in the third decade of life, where the mean age of the patients with GG was 28 years. These results were similar to those described in the literature regarding PG (22). Observation is the treatment of choice in most cases, in which maintenance of oral hygiene and the use of soft toothbrushes is mandatory and adequate to avoid haemorrhage, since, after delivery, a steady reduction in the size of the lingual mass, until total regression, has been described (23).

Nevertheless, if the lesion represents the cause of speech and mastication interference or bleeding, surgical excision is required. Treatment can be performed with scalpel, pulsed laser surgery, cryosurgery, radiosurgery and intralesional injection of sodium tetradecyl sulphate, ethanol or corticosteroids (5, 24). If uncontrolled bleeding occurs, management should include even induction of labor to save patient’s life (25, 26).

It is clear that in every case a careful risk – benefit assessment is mandatory prior any surgical treatment is carried out. In our case, the patient referred interference in speech and mastication; she did not present comorbidities or major contraindications and so we decided to perform excision in order to prevent bleeding. Because of the site of origin, it was possible to remove the lesion under local anesthesia using scalpel without additional risk for the patient. Even in such cases surgical excision can be safely performed, the best “treatment” remains prevention, including regular brushing of the teeth using soft toothbrushes and dental floss coupled with routine dental check-ups and plaques removal during pregnancy (25).

Disclosure

None of the Authors has anything to disclose.

References

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