Title
Localized juvenile spongiotic gingival hyperplasia: A report of 27 cases

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Title: Localized Juvenile Spongiotic Gingival Hyperplasia: A Report of 27 Cases.

Abstract

Background: Localized juvenile spongiotic gingival hyperplasia (LJSGH) is a poorly understood but distinctive inflammatory hyperplasia occurring in children and young adults. Less than 100 cases have been reported since its initial description.

Methods: During the period of 2015-2018, cases of LJSGH were identified, retrieved and their clinical and histopathological data reviewed.

Results: There were 27 cases with a median age of 13 years (range 7-72 years). Twenty-four of 27 patients were less than 20 years old, and in 3 cases the patients were over 60 years of age. The most commonly affected site was the anterior maxillary gingiva presenting as a solitary, red, and papillated lesion. Typical microscopic findings included elevated areas of variably acanthotic, spongiotic non-keratinized epithelium with elongated rete ridges, accompanied by a neutrophilic rich infiltrate. An abrupt transition between epithelium affected by LJSGH and normal mucosa was characteristic. LJSGH typically exhibited full thickness epithelial expression of CK19 without expression of estrogen and progesterone receptors.

Conclusions: The clinical and histopathologic characteristics of LJSGH are unique and consistent. Despite the name, the condition is not limited to juveniles and can occur in adults. LJSGH in adults and juveniles shares the same spectrum of histopathologic and immunohistochemical findings.

Keywords: Oral disease, gingival lesion, gingivitis, inflammatory gingival hyperplasia

Introduction

Localized juvenile spongiotic gingival hyperplasia (LJSGH) is a rarely encountered, poorly understood but distinctive form of inflammatory hyperplasia with less than 100 cases reported in the literature. In 2007, Darling et al. [1] first described the condition using the monicker of “juvenile spongiotic gingivitis” to highlight its spongiotic and inflammatory nature. The term “localized juvenile spongiotic gingival hyperplasia” (LJSGH) was subsequently introduced by Chang et al. [2] to emphasize its localized clinical nature and hyperplastic morphology seen on microscopy.

Affecting the gingivae, LJSGH most often occurs in children and young adults [1,2]. In contrast to conventional plaque-associated gingivitis and puberty-associated gingivitis, LJSGH is typically resistant to oral hygiene measures [1,2]. The diagnosis of LJSGH requires a high index of suspicion on the part of the clinician and pathologist alike to exclude similar appearing inflammatory gingival lesions. However, no previous report of LJSGH was found in previous dermatology publications. To increase awareness, further describe this condition, and offer additional insights, we identified 27 cases of LJSGH and reviewed the clinical, microscopic, and immunohistochemical findings.

Methods

This study was approved by our Institutional Review Board (IRB). From the period of 2015-2018, we identified cases of LJSGH from the files of our institution. Clinical and demographic information including age, gender, anatomical location, and clinical features were collected. Hematoxylin and eosin stained slides and corresponding immunochemical stained sections were reviewed. All cases had been immunostained with cytokeratin 19 (CK19), estrogen receptor, and progesterone receptor as described previously [1].

Results

We reviewed slides that were diagnosed as LJSGH, and identified 27 patients who met the criteria for LJSGH described by Darling et al. [1] and Cheng et al. [2]. The demographic information and clinical findings are summarized in Table 1. Twenty-four patients were less than 20 years of age, and 3 patients were older than 60 years of age. The median age was 13 years (range 7-72 years) with a predominance of males (17/27; 63%). Reported duration of the condition prior to biopsy ranged from 3 months to greater than 7 years. The most commonly involved site was the anterior maxillary gingiva, and it most commonly present as a red, bleeding, and papillated lesion without pain. Additional reported features included ulceration, bleeding, soreness, an intermittent clinical course, irregular margins, firmness, and exophytic or hyperplastic quality. The largest reported size was 1 cm lesion in the greatest dimension. The clinical diagnoses included developmental gingivitis, plasma cell gingivitis, pyogenic granuloma, giant cell granuloma, granulation tissue,

gingival hyperplasia, hemangioma, peripheral ossifying fibroma, and fibroma not otherwise specified.

The histological and immunological findings are summarized in Table 2. LJSGH has a consistent histopathology showing elevated areas of non-keratinized, variably acanthotic stratified squamous epithelium that exhibited spongiosis, elongation of rete pegs, atrophy of the epithelium overlying long connective tissue papillae, and a neutrophilic infiltrate. Depending on orientation of the specimen there was a characteristic sharply demarcated border between lesional tissue and adjacent unaffected gingiva. All cases showed full thickness epithelial expression of CK19, but were uniformly negative for estrogen and progesterone receptors. All three adult cases demonstrated identical microscopic findings and immunohistochemical staining properties compared to those seen in the juvenile cases (Figures 2, 3).

Discussion

LJSGH is a distinct entity limited to the gingiva with, to date, less than 100 cases reported in the literature. This rarity is likely an underestimation due to its clinical and microscopic similarity to other diseases and is also likely impacted by clinicians' and pathologists' unfamiliarity with this relatively newly described entity. Here, we report 27 additional cases of LJSGH to offer additional insights into the disease. A total of 27,901 oral cases were reviewed by our institution between 2015 and 2018, during the study time period. To our knowledge, this is the first report of LJSGH in the dermatology literature.

As its name suggests, LJSGH is most often described in juveniles. Darling et al. [1] reported that 17 of their 24 (71%) patients were between 10 and 14 years old, while Chang et al. [2] and Allon et al. [3] reported that 28 of 51 (55%) patients and 7 of 10 (70%) patients were between 11 and 15 years old, respectively. In this current study, we found that all but 3 patients were less than 20 years of age with 29.6% of the patients younger than 10 years old, and 44.4% of the patients between 11 and 15 years. The majority of patients within other prior publications are also between 11 and 15 years [4-6]. Vargo et al. [7] reported a large age range between 3 to 64 years old, with the median to be 14.5 years old. The median age in our series was 13 years old. Together with the previous case series [1-8], we conclude that LJSGH is most common to but not limited to the juvenile age range.

Cases of LJSGH have been reported in adults but there have been no other reports of this disease in patients over 40 years old. Darling et al. [1], Chang et al. [2], Argyris et al. [4], and Siamantas et al. [8] each reported the condition in one adult between the ages of 19 to 40. Vargo et al. [7] described ten adults between the ages of 18 to 64. In our study, we identified 3 adults with ages of 65, 66, and 72, who presented gingival lesions that were clinically, morphologically, and immunohistochemically identical to LJSGH. Hence, the age range of LJSGH is likely

much wider than previously believed, and we expect that as further cases in adults are described the recognized age range of the condition might increase.

Prior reports have described varying female to male ratios of 1:1 in one series of 24 patients, 2.3:1 in a series with 51 patients, 1:1 in a series of 10 patients, 1.25:1 in a series of 28 patients, 0.5:1 in a series of 21 patients, and 0.5:1 in a series of 3 patients [1-4, 6, 7]. In our series of 27 patients, we found a slight male predominance with a female to male ratio of 0.6:1. When prior reports are aggregated with our series a balanced gender ratio emerges, with a female to male ratio of 1:1, suggesting that sex hormones are likely unrelated to the etiology of LJSGH.

Similar to previous reports [1-8], the most commonly affected oral site for LJSGH was the anterior maxillary gingiva. The reason for this localization in the anterior maxilla is unknown. In a new finding, we identified patients with LJSGH affecting other intraoral sites including the posterior maxillary and posterior mandibular gingivae. We can offer no explanation for this but increased awareness of the condition and enhanced vigilance on the part of the clinicians might be a factor.

The clinical presentation of LJSGH in our series was as a solitary, red, and papillated lesion that may be ulcerated or bleed. The course can be waxing and waning or progressively enlarging. LJSGH can be otherwise asymptomatic or be associated with soreness. Other clinical features include irregular margins, firmness, and exophytic or hyperplastic qualities. Due to these findings, the clinical differential diagnosis can include puberty related gingivitis, plaque-related gingivitis, pyogenic granuloma, giant cell granuloma, hemangioma, and peripheral ossifying fibroma.

In our series, the microscopic findings of LJSGH from both child and adult patients included elevated areas of spongiotic and variably acanthotic, non-keratinized stratified squamous epithelium, with elongated rete ridges and atrophy of the epithelium overlying long connective tissue papillae. While a neutrophilic infiltrate is invariably present, a plasma cell-rich infiltrate sometimes containing eosinophils can be observed. The abrupt transition between epithelium affected by LJSGH and normal mucosa was characteristic, and this is a histopathological observation that has not been previously described. There are morphological similarities between LJSGH and cutaneous clear cell acanthoma, including sharp margination, acanthosis, thin supra-papillary plates, and intraepithelial netrophils. However, clear cell acanthoma is characterized by glycogen-rich squamous epithelium, whereas LJSGH is characterized by a spongiotic squamous epithelium that lack PAS-staining (Figures 2D, 3D).

CK19 is expressed in all layers of the epithelium in the absence of estrogen and progesterone receptor expression in LJSGH. By contrast, the more common puberty gingivitis is CK19 positive but also expresses progesterone and estrogen receptors

while plaque-related gingivitis is negative for all three markers. Additional differences between pyogenic granuloma and these disease processes are summarized in Table 2 [9-12]. CK19 expressioin is not present within clear cell acanthomas [13]. It has been hypothesized that the CK19 expression is due to the odontogenic origin of LJSGH [1]. CK19 expression has been theorized to be a sign of impending carcinogenesis of oral mucosa, due to its increased expression in hyperplastic lesions, and its expression continues in dysplastic and malignant lesions [~~13~~14]. Epithelial dysplasia is absent in LJSGH from all of our juvenile and adult patients, thus LJSGH is not likely to be a premalignant condition. Furthermore, evidence presented by Argyris et al. concluded that human papillomavirus does not participate in the pathogenesis of LJSGH [4].

Unlike puberty and plaque-related gingivitis, LJSGH is reported to not respond to conventional oral hygiene measures such as brushing and flossing [1,2]. There is potential for LJSGH to recur after biopsy procedures. Localized ablative procedure such as cryotherapy has been reported effective for the treatment [~~14~~15], which would be reasonable to consider when the lesion is symptomatic or is cosmetically unsightly. The therapeutic effect of topical steroid therapy has been reported to be transitory [~~15~~16]. For cases of asymptomatic lesions, observation would be viable for this benign entity.

Conclusions

LJSGH is an infrequently encountered entity that is commonly a lone, red, papillated lesion located on the anterior maxillary gingiva. It can affect both children and adults over a wide range of ages, and has no strong predilection towards a gender. Microscopically, LJSGH is characterized by epithelial acanthosis and spongiosis, with neutrophilic infiltrate and sharp marginations from the surrounding tissue. Full-thickness epithelial CK19 expression is a constant finding, and when coupled with progesterone and estrogen receptor findings, LJSGH can be differentiated from puberty and plaque-related gingivitis.

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Tables

Table 1: Localized juvenile spongiotic gingival hyperplasia (LJSGH) demographic and lesional characteristics

Age group	**Numbers (%, N=27)**
<=10	8 (29.6%)
11-15	12 (44.4%)
16-20	4 (14.8%)
21-60	0 (0.0%)
>=61	3 (11.1%)
Median age	**13 years**
Average age	**18 years**
Gender	**Numbers (%, N=27)**
Male	17 (63.0%)
Duration prior to biopsy†	**3 months to over 7 years**
Anatomical location	**Numbers (%, N)**
Maxilla	23 (85.2%, N=27)
Anterior	24 (92.3%, N=26)
Right	18 (72%, N=25)
Left	5 (20%, N=25)
Midline	2 (8%, N=25)
Clinical features‡	**Numbers reported§**
Red color	20
Papillated	6
Asymptomatic	5
Growth	3
Bleeding	2

† Duration prior to biopsy is reported in nine patients.

‡ Other reported features include ulceration, soreness, waxing-waning course, irregular margins, firm, pedunculated, and exophytic/hyperplastic quality.

§ Each of the clinical features is not reported in all twenty-five patients.

Table 2: Comparison of localized juvenile spongiotic gingival hyperplasia (LJSGH) with its differential diagnoses

Disease	Age group	Archetypal location	Typical clinical appearance	Microscopic features	IHC properties	Response to oral hygiene
Localized juvenile spongiotic gingival hyperplasia	Primarily juveniles, with few presenting as elderly adults	Localized to attached anterior maxilla	Red, bleeding, asymptomatic, and papillated growth	Sharply marginated spongiosis and hyperplasia with elongation of rete pegs, atrophy of the epithelium overlying long connective tissue papillae, and a neutrophilic infiltrate	CK19+, ER-, PR-	No
Puberty associated gingivitis	Juveniles only	Generalized on marginal gingiva	Inflamed, bleeding, and tender gingiva, sometimes with hyperplasia	Spongiosis and acanthosis with elongation of rete pegs, atrophy of the epithelium overlying long connective tissue papillae, and a neutrophilic infiltrate	CK19+, ER+, PR+	Yes
Plaque-associated gingivitis	All age groups	Generalized, originates from gingival margin and spreads to the entire gingiva	Inflamed, bleeding, and tender gingiva, sometimes with hyperplasia	Inflamed fibrous and granulation tissue	CK19-, ER-, PR-	Yes
Pyogenic granuloma	All age groups, most prominently in young adults	Localized to marginal anterior maxilla	Red, bleeding, smooth or lobulated, and compressible growth	Vascular proliferation that resembles granulation tissue	N/A	No

IHC, immunohistochemical; ER, estrogen receptor; PR, progesterone receptor; N/A, not applicable.

Figure legends

Figure 1: Localized juvenile spongiotic gingival hyperplasia usually presents as a solitary, red, papillated lesion on the anterior maxillary gingiva.

Figure 2: Localized juvenile spongiotic gingival hyperplasia (LJSGH) histological characteristics in pediatric patients. A, The slightly mamillated to papillated nonkeratinizing epithelium is spongiotic and acanthotic, with an abrupt transition between epithelium affected by LJSGH and normal mucosa (original magnification 100x, H&E). B, Elongated connective tissue papillae are filled with neutrophils that infiltrate the spongiotic epitihelium (original magnification 200x, H&E). C, Immunohistochemistry demonstrates full thickness epithelial Cytokeratin 19 expression with an abrupt transition between epithelium affected by LJSGH and normal mucosa (original magnification 100x, CK19). D, Periodic acid–Schiff ~~Progesterone receptor A~~ stain ~~is negative~~demonstrates a lack of glycogen deposition in LJSGH (original magnification ~~100x~~200x, PRA).

Figure 3: Localized juvenile spongiotic gingival hyperplasia (LJSGH) histological characteristics in adult patients. A, The slightly mamillated to papillated nonkeratinizing epithelium is spongiotic and acanthotic, with an abrupt transition between epithelium affected by LJSGH and normal mucosa (original magnification 100x, H&E). B, Elongated connective tissue papillae are filled with neutrophils that infiltrate the spongiotic epitihelium (original magnification 200x, H&E). C, Immunohistochemistry demonstrates full thickness epithelial Cytokeratin 19 expression with an abrupt transition between epithelium affected by LJSGH and normal mucosa (original magnification 100x, CK19). D, Periodic acid–Schiff ~~Progesterone receptor A~~ stain demonstrates a lack of glycogen deposition ~~is negative~~ in LJSGH (original magnification ~~100x~~200x, PRA).