# Distinctive aspects of oral hyaline ring granulomas

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The hyaline ring granuloma is a distinct oral entity characterized as a foreign body reaction occurring either centrally or peripherally. The granulomas may assume different histological characteristics, possibly related to the length of time in the tissue, and adequate recognition is important to avoid misdiagnosis. The aim of this article was to report 3 cases of hyaline ring granulomas with distinctive clinical and histopathological aspects, discussing the reasons for the different histological findings. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;106:e35-e39)

The hyaline ring granuloma is an uncommonly reported oral finding with undefined etiology.<sup>1,2</sup> Many authors consider a vegetable origin, although others deny this possibility.<sup>1,3,4</sup> Nevertheless, a similar condition described as pulse granuloma is usually observed in the lungs and alimentary tract and rarely in the gallbladder, fallopian tube, and skin.<sup>5</sup> Since the etiology of the hyaline rings is somewhat controversial, it seems more reasonable to use a descriptive term rather than any other which may indicate its origin. Most of the lesions are asymptomatic and occur in edentulous areas, but some discomfort may be reported, especially with central lesions.<sup>6</sup>

Fewer than 80 cases of oral hyaline ring granulomas have been reported with a scant intent of defining its etiology.<sup>1,2,7,8</sup> Less attention, however, was given to the histological aspects, which may vary with the time of evolution and location. We report 3 cases of hyaline ring granulomas, highlighting the distinct clinical and histopathological aspects.

### CASE 1

An edentulous 48-year-old white female complained of a painless maxillary nodule of 6 months' duration. The patient was otherwise healthy and failed to report

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previous trauma or surgery in the region. Her general medical history was noncontributory. Intraorally, a well-circumscribed sessile nodule covered by normal mucosa and measuring  $3.0 \times 0.7$  cm was seen on the edentulous right maxillary ridge. The main clinical diagnosis was fibrous hyperplasia and, under local anesthesia, an excisional biopsy was performed. The specimen was submitted to histopathological analysis, which revealed an intact epithelium and proliferation of dense connective tissue with a mild chronic cellular inflammatory infiltrate. External and adjacent to surface epithelium, a superficial slit-like cavity contained a well preserved vegetable-like eosinophilic material associated with hyaline rings (Fig. 1, A). The rings were seen as round structures enclosing amorphous material consistent with degenerated starch cells and were closely associated with the presence of the vegetable particles. The rings were periodic acid-Schiif (PAS) stain positive and diastase resistant (Fig. 1, D). The microscopic aspect was compatible with inflammatory fibrous hyperplasia and vegetable particle implantation in the surface. Scanning electron microscopy (SEM) revealed a surface structure closely resembling vegetable tissue, supporting the hematoxylin & eosin (H&E) stain findings (Fig. 2).

### CASE 2

An 82-year-old Caucasian male patient was referred because of a complaint of a 1-year duration tongue lesion. His general medical history was noncontributory. Intraoral examination revealed gingivitis and poor oral health associated with hypossalivation and inadequate control of tongue movements. There was also a  $1.5 \times 1.0$ -cm painful firm nodule covered by normal mucosa in the anterior middle third of the dorsum of the tongue. It was reportedly caused by chronic trauma from a previous habit of forcing a toothpick against the dorsum of tongue. The provisional clinical diagnosis

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Fig. 1. **A**, Histological aspect of case 1, resembling a vegetable particle (H&E, original magnification  $\times$ 5). **B**, Histological aspect of case 2. Multiple hyaline rings inducing a foreign body granuloma formation (H&E; OM  $\times$ 10). **C**, Histological aspect of case 3. Hyaline ring within a granuloma full of foamy macrophages (H&E; OM  $\times$ 10). **D**, Case 1. PAS-positive diastase-resistant stain on the periphery of the foreign body, showing the peripheral hyaline rings intensely stained (PAS; OM  $\times$ 5). **E**, Cases 2 and 3. PAS-positive diastase-resistant staining of the hyaline rings in the central area of a granuloma (PAS; OM  $\times$ 10). **F**, Case 3. Focal area positive for PAS and diastase-resistant stain (PAS, OM  $\times$ 40).



Fig. 2. A, Scanning electron microscope (SEM) picture of the foreign body of case 1, resembling a vegetable particle (SEM;  $\times$ 150). B, High-power view of Fig. 2, A, showing a central area typical of a seed (SEM;  $\times$ 1600).

included reactive process and benign mesenchymal tumor. An excisional biopsy under local anesthesia was performed. Microscopic examination revealed a fragment of oral mucosa covered by normal epithelium and abundant dense collagenized connective tissue. Skeletal muscle fibers were embedded in a background of stromal fibrosis, and focal areas of hyalinized collagen bundles with granulomas containing multinucleated Langhans-type and foreign-body giant-type cells associated with hyaline rings were observed. The hyaline



Fig. 3. A, Case 2. Macrophages and giant cells showing immunoreactivity for CD 68. Red arrow shows degenerated sketetal muscle fibers CD68 negative (IHC, OM  $\times 10$ ). B, Case 2. Immunoreactivity for desmin in normal and degenerated skeletal muscle fibers (*black arrow*). Red arrow points to giant cells, desmin negative (IHC, OM  $\times 10$ ).

rings were located deep inside the connective tissue (Fig.1, B) and resembled vegetable particles, showing intense amorphous eosinophilia and a PAS-positive, diastase-resistant cell wall (Fig. 1, E). The inner material was weakly stained by hematoxylin and eosin, similar to case 1. Muscle degeneration, possibly associated with scar formation, was observed proximal to the granulomas, thereby mimicking multinucleated giant cells and containing occasional scattered inclusionlike bodies. Congo red stain under polarized light examination was negative. Moreover, immunohistochemical (IHC) analysis for CD68 (PG-M1, Dako Corp., Carpenteria, CA, USA, 1:400) and desmin (D33, Dako Corp., 1:1000) was performed. The CD68 showed positivity in giant cells and epithelioid macrophages within and adjacent to hyaline rings (Fig. 3, A), and the desmin highlighted atrophic and normal skeletal muscle fibers adjacent to the granulomas (Fig. 3, B). The histological aspects were consistent with fibrous hyperplasia with some areas of hyaline ring granulomas of probable vegetable particle origin. The patient recovered uneventfully and revealed no signs of recurrence after 8 months.

# CASE 3

A 47-year-old female Caucasian patient was referred because of dental pain associated with an extensively destroyed tooth. The patient was otherwise healthy, and her general medical history was noncontributory. Periapical radiographic evaluation revealed a radiolucent area adjacent to the apex of the right superior second premolar, which was subsequently extracted. Microscopic analysis of the periapical lesion revealed connective tissue with chronic cellular inflammatory infiltrate, abundant xanthomatous macrophages, and scattered multinucleated foreign-body giant cells, rendering a diagnosis of periapical granuloma. Interestingly, inside of the periapical lesion, there was a focal area of hyaline rings with amorphous material surrounded by foamy macrophages and multinucleated giant cells, characterizing a foreign-body granuloma (Fig. 1, *C*). The hyaline rings were PAS-positive and diastase-resistant (Fig. 1, *F*). IHC analysis for CD68 highlighted xanthomatous macrophages and multinucleated giant cells.

## DISCUSSION

The oral hyaline ring granuloma is an uncommon entity with unclear etiology. Dunlap and Barker<sup>9</sup> were among the first authors to evaluate this entity and considered it to be an acute vasculitis, naming it "giantcell hyalin angiopathy." Their proposal was not completely accepted, and Mincer et al.<sup>4</sup> classified the hyaline rings as inclusion of cooked vegetable particles, calling it "pulse granulomas." Other terms proposed later, such as "oral vegetable granuloma" and "legumeassociated lesion," also addressed its vegetable origin. Disagreement regarding its etiology has been observed, and other investigators also considered the rings as degenerated collagen fibers or fibrosed extravasated proteins of unknown origin.<sup>1,2</sup> To promote a unique nomenclature, Chou et al.<sup>7</sup> proposed the descriptive term "hyaline ring granuloma," which seems more suitable and also avoids misunderstanding. We prefer this descriptive term as there is still an important lack of agreement regarding its origin. This doubt resides in one important question: Is the hyaline ring composed of degenerated vegetable particles, or is it a consequence of chronic inflammation? While a clear explanation of the entity's etiology remains elusive, it seems adequate to use a histologically descriptive term, such as hyaline ring granuloma. Similar lesions associated with vegetable particles implantation have been described in the lungs and gastrointestinal tract and, more rarely, on the skin, gallbladder, and fallopian tubes.<sup>5</sup> These particles behave as foreign bodies stimulating granuloma formation.

Since 1970, when Lewars<sup>8</sup> called these oral lesions "chronic periostitis," the possible food origin has been considered. This theory was initially proposed by comparing oral lesions to pulmonary pulse granulomas, which result from aspiration of vegetable particles. At that time, the high resistance to tissue-phagocyte digestion was considered as the cause of the granulomas.<sup>3</sup> To confirm its etiology, several ultrastructural studies have been performed but with conflicting results. Chen et al.<sup>1</sup> proposed a 3-stage process for the hyaline ring formation: (1) pooling and coagulation of extravasated serum proteins in areas of trauma, (2) ring arrangement around the coagulum of proteins, and (3) solidification of the hyaline body, thus causing the entrapment of fibroblasts within the ring. Harrison and Martin,<sup>2</sup> by contrast, observed a close similarity between hyaline rings and vegetable cell walls, proposing the latter as the basis of the rings since collagen microfibrils are similar to those of cellulose.

The pathogenesis of hyaline ring granuloma has also been evaluated by inducing its formation in animal model. Implantation of homogenized lentils in the orofacial region of Sprage-Dawley rats was followed by progressive degenerative changes, and, after 6 months, only a few well-preserved lentil cells could still be seen in the lesions.<sup>1</sup> More giant cells were seen in initial lesions than in older ones, which showed droplet calcifications within the eosinophilic masses. Hyaline rings were PAS-positive with strong staining in cellulose envelopes and frameworks. No PAS-positive grain was observed due to rapid digestion of starch. All hyaline rings, as well as the associated vegetable structures, were discreetly birefringent under polarized light. Histochemical and IHC analyses were performed with adequate positive and negative controls. Based on these results, it is probable that human lesions are caused by traumatic implantation of vegetables particles in an extraction socket or oral ulcer with cellulose being responsible for granuloma formation as was found in our cases 2 and 3. The intense PAS-positive, diastaseresistant staining of the ring wall is associated with the presence of cellulose, which seems to be responsible for the granuloma formation.<sup>3,4</sup> Starch cells are scarce since they are quickly digested, and giant cell inclusions are usually observed in oral lesions, in contrast to granulomas from lungs and gut.<sup>7</sup>

Ultrastructural studies have also been performed in order to clarify the hyaline ring origin, but there is no agreement on their findings. Because of the presence of a biphasic pattern of the hyaline ring (cross-banded fibrils in the outer part and non-banded fibrils in the inner part), Chen et al.<sup>1</sup> considered it to be a pooling and coagulation of extravasated serum proteins. Another study with similar methodology considered it to be degenerated collagen.<sup>10</sup> Nevertheless, Harrison and Martin<sup>2</sup> compared vegetable tissue with glutaralde-hyde-fixed oral specimens and concluded that they were closely similar. Our SEM study in case 1 reinforces these findings.

The 3 cases reported herein show distinctive histopathological aspects, all with granulomatous giant cell reaction and hyaline ring formation. Case 1 shows superficial hyaline rings adjacent to a lentil, while case 2 displays a similar hyaline ring in a deeper location, probably related to the habit of forcing the toothpick against the dorsum of tongue. Case 3 has a degenerated amorphous ring that still has external PAS positivity and was probably introduced in the periapical region through the extensive carious lesion. Talacko and Radden<sup>3</sup> observed that degeneration of vegetable material implanted into the submucosa and mandible of rats was time-dependent. The different microscopic features of all our 3 cases may be associated with distinct evolutive periods.

Case 2 showed interesting histological features with areas of degenerative skeletal muscle fibers mimicking multinucleated giant cells. Immunoreactivity for desmin strongly marked these fibers, and the lack of evident cytoplasmic inclusions as well as negative Congo red staining under polarized light suggests that the diagnosis of inclusion body myositis is highly unlikely.<sup>11</sup> Muscular degeneration associated with granulomatous response can also be classified as granulomatous myositis, but the foreign body presence excludes this diagnosis.<sup>11</sup> Hence, it seems that chronic inflammation and stromal fibrosis is responsible for muscular degeneration, and the presence of two distinct populations of (1) epithelioid macrophages and giant cells (CD  $68^+$ ) together with (2) desmin-positive degenerative muscular fibers resembling giant cells confirms this hypothesis. The hyaline rings were negative to both antibodies, highlighting their foreign origin.

The findings presented here suggest that these 3 cases represent different evolutive stages of the same lesion, case 1 being the most recent and case 3 the most ancient. They reflect the presence of foreign body implantation, possibly of vegetal origin, at different tissue

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depths. Case 1 seems to have been a superficial soft tissue foreign body implantation, while case 2 was a deep presentation, possibly caused by toothpick trauma. Case 3 was possibly caused by vegetable implantation, in a previous lesion of periapical granuloma, through an exposed root canal as described by Dunlap and Barker.<sup>9</sup> Once a granulomtous response has occurred, chronic exposure to inflammatory enzymes probably modifies the morphological aspects of the hyaline rings without compromising its antigenic potential.

In summary, hyaline ring granulomas are well-described entities with distinctive histopathological aspects but an unclear etiology. Oral vegetable implantation has distinct histopathological aspects from pulse granulomas of the lungs and gut, as starch cells are often absent and giant cells may be scant. Once it promotes and maintains chronic inflammation, however, it can be responsible for a distinct and persistent histological evolution, especially in an intraosseous location.

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