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Sociedad Gallega de Otorrinolaringología  
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## **Caso Clínico**

**Idiopathic Lymphoid Hyperplasia:  
a role for commensal microbiota?**

**Hiperplasia linfoide idiopática:  
uma associação com o microbioma?**

Joana Silva<sup>1</sup>, Bruno Domingues<sup>1</sup>, Rita Gama<sup>1</sup>,  
Sandra Gerós<sup>1</sup>, Eugénia Castro<sup>1</sup>, Artur Condé<sup>1</sup>

<sup>1</sup> Department of Otolaryngology,  
Centro Hospitalar Vila Nova de Gaia/Espinho,  
Porto, Portugal  
Rua Conceição Fernandes 1282  
4434-502 Vila Nova de Gaia,  
Porto, Portugal

Corresponding Author: Joana Silva  
Department of Otolaryngology,  
Centro Hospitalar Vila Nova de Gaia/Espinho,  
Porto, Portugal

Rua Conceição Fernandes 1282  
4434-502 Vila Nova de Gaia, Porto, Portugal  
Tel: +351 912443623  
E-mail: joanavilela.silva@gmail.com

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Correo electrónico:  
[actaorlgallega@gmail.com](mailto:actaorlgallega@gmail.com)

## Resumo

A hiperplasia linfóide é uma lesão reativa de tecido linfóide, considerada o equivalente extranodal de um linfonodo reativo.

Embora a etiopatogenia desta entidade seja incerta, a sua associação com a colonização da mucosa por estirpes bacterianas específicas foi previamente descrita por alguns autores.

Neste trabalho relatamos dois casos clínicos de hiperplasia linfóide reativa, indistinguíveis de malignidade, e discutimos a interação entre o microbioma e o hospedeiro, que poderá contribuir para o aparecimento deste tipo de lesões.

## Palavras chave

Hiperplasia linfóide; actinomyces; microbioma; hipertrofia amigdalina.

## Abstract

Lymphoid hyperplasia is a reactive lesion of lymphoid tissue, considered the extranodal equivalent of a reactive lymph node.

Although its etiology remains elusive, mucosal colonization with specific strains of bacteria was previously proposed in the literature as a possible etiologic agent.

In this paper, we report two clinical cases of reactive lymphoid hyperplasia, indistinguishable from malignancy, and we discuss the interaction between the microbiome and the epithelial lining that may contribute to the etiology of this condition.

## Keywords

lymphoid hyperplasia; actinomyces; microbiome; tonsillar hypertrophy.

## Introduction

Lymphoid hyperplasia (pseudolymphoma) is a reactive lesion of lymphoid tissue, considered the extranodal equivalent of a reactive lymph node.<sup>1</sup>

While this condition is often asymptomatic in adults, it can present with unspecific symptoms including throat pain, dysphagia and foreign body sensation.<sup>2</sup> Clinical examination reveals lymphoid hypertrophy in a wide range of size and shape morphology, sometimes indistinguishable from malignant lesions.<sup>1</sup>

Several factors including pharyngolaryngeal reflux, obesity, gender, age, and smoking are associated with this condition, however, its etiology remains elusive.<sup>3</sup>

In healthy individuals, immunity allows mucosal colonization by commensal microorganisms, while preventing epithelial invasion and infection. As a first line defense mechanism, tonsillar hypertrophy may occur as a response to increased antigenic stimulation and a role for commensal microflora in tonsillar disease has been previously proposed.<sup>4</sup>

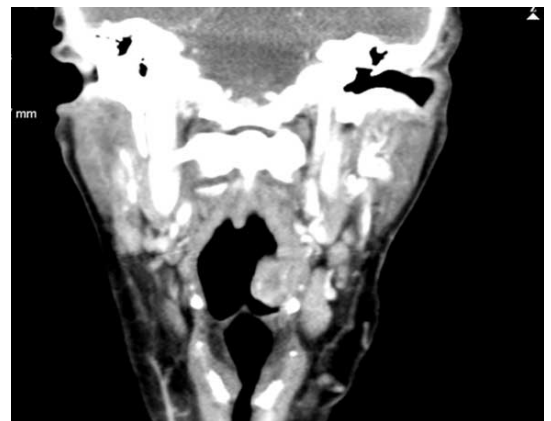
In this paper, we report two clinical cases of reactive lymphoid hyperplasia, indistinguishable from neoplasia and we discuss the interaction between the microbiome and the epithelial lining that may contribute to the etiology of this condition.

## Clinical Case 1

A 59-year-old woman presented with a history of occasional bloody sputum for the last six years. These episodes occurred monthly with associated episodic cough and she did not present any other complaint. Her medical history included a tonsillectomy during childhood and chronic *Helicobacter pylori* positive gastritis. She had no smoking or alcohol intake habits.

Her global status was excellent and no suspicious findings were evident on physical examination.

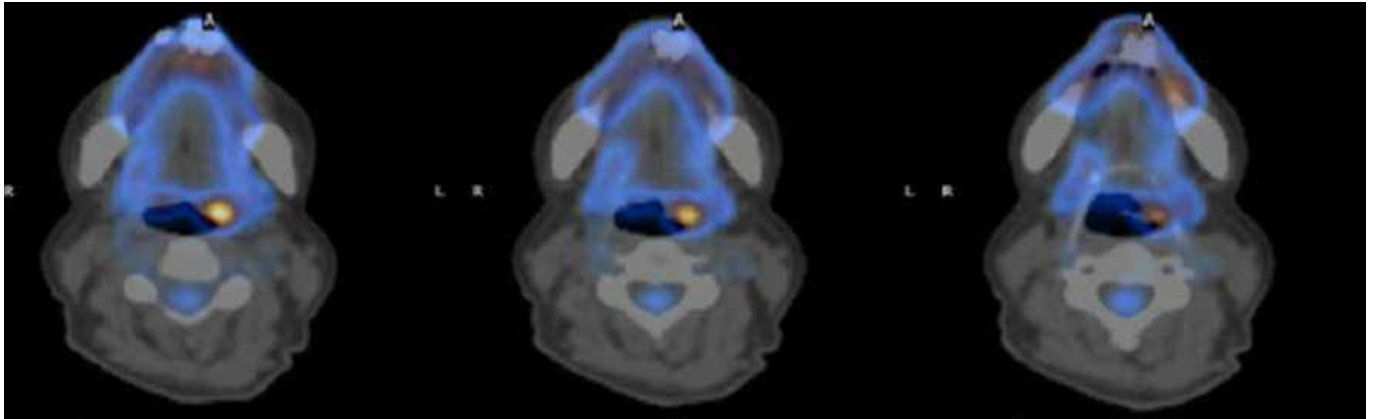
Initial management included an overall biochemistry and hematology screening, coagulation study, a urinalysis, chest radiography and an upper gastrointestinal endoscopy, which were all normal, and a cervicothoracic computed tomography (CT) scan (Figure 1). The latter revealed a lesion on the left palatine tonsil with 2 cm extending to the left vallecula and pharyngoepiglottic fold, with suspicious tongue base infiltration. A contrast-enhanced adenopathy on the area IIA was suspicious of metastatic involvement. She was then referred to our Otolaryngology outpatient clinic for further characterization. We noticed an enlargement of the left tongue base with left vallecular obliteration (Figure 2), but tongue movement was preserved and no masses or adenopathies were palpable.



**Figure 1. Cervical CT scan showing a left tonsillar mass.**



**Figure 2. Fiber optic laryngoscopy view displaying asymmetric lingual tonsil.**



**Figure 3. Left tonsillar 18-FDG uptake on PET scan.**

We requested an MRI and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan (Figure 3).

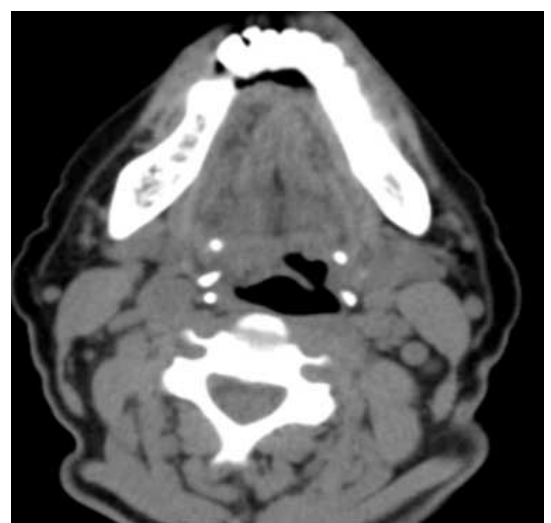
The MRI confirmed the exophytic mass previously described, which was not dissociative from lingual lymphoid tissue and the PET scan revealed intense uptake in these areas. Histopathological examination of the lesion sample revealed lymphoid follicular hyperplasia with colonies of *Actinomyces* but no evidence of dysplasia or tumoral cells. Serologies for HIV (human immunodeficiency virus) 1 and 2, EBV (Epstein-Barr virus), and CMV (cytomegalovirus) were negative.

The patient had an extended biopsy and revision tonsillectomy. Histopathological examination again revealed lymphoid follicular hyperplasia.

A watchful waiting approach was undertaken with repeated MRI. The patient remained asymptomatic and no evident growth was apparent on follow-up. The definitive cause for hemoptysis was not identified.

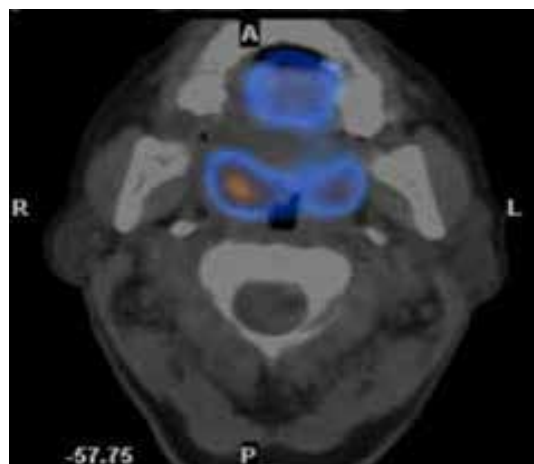
## Clinical Case 2

A 57-year-old woman presented with persistent pharyngeal globus and intermittent throat pain of two months duration. Apart from a single episode of blood-stained saliva, she denied other pharyngeal symptoms. Her medical history included dyslipidemia and osteoarthritis and an ongoing work up for significant weight loss over the last four months. She had no smoking or alcohol intake habits. A complete otolaryngologic examination was performed discovering erythematous pharyngeal walls with a cobblestone appearance and an enlarged lingual tonsil on the right side, partially obliterating the vallecula. Cervical CT scan (Figure 4) revealed an enlarged right palatine tonsil and suspicious right level II adenopathies with 14mm. A PET-scan showed uptake on the right palatine tonsil and the adenopathies described (Figure 5). Serologies for HIV 1 and 2, EBV, and CMV were negative. She was submitted to tonsillectomy and tongue base biopsy which discovered reactive lymphoid follicular hyperplasia with *Actinomyces*.



**Figure 4. Right palatine tonsil hyperplasia effacing ipsilateral vallecula on CT scan.**

*ces* colonies. Symptoms abated spontaneously and a partial weight gain was noted. Asymmetric tongue base and pharyngeal cobblestone appearance remained unchanged and there was no evidence of oropharyngeal malignancy on follow-up.



**Figure 5. Focal 18-FDG uptake by the right palatine tonsil.**

## Discussion

Lymphoid hyperplasia occurs due to an increase in lymphoid elements. These elements include B and T lymphocytes, and dendritic cells that proliferate in response to rising antigenic stimulation, thus contributing to an increase in tonsillar size and weight. The tonsil size has been shown to be directly proportional to the mean oropharyngeal bacterial load.<sup>4</sup>

Though an increased bacterial load contributes to an overall increase in antigenic load, the global number of bacteria is not the only determinate factor. Indeed, the presence of specific bacteria such as *Haemophilus Influenza*, *Streptococcus pyogenes*, and *Actinomyces* in tonsillar tissue was associated with increased tonsillar weight.<sup>4</sup> Also, the ability of specific bacterial strains to reprogram immune cells and alter their differentiation was demonstrated in the small intestine mucosa.<sup>5</sup>

*Actinomyces* colonization was found to be increased among children with tonsillar hypertrophy and obstructive tonsillar disease who had tonsillectomy when compared with children who had surgery for recurrent tonsillitis.<sup>6</sup> Other authors, however, have failed to confirm the association between *Actinomyces* colonization and lymphoid hyperplasia. Of note, in these cases, colonization was not associated with mucosal inflammatory reaction.<sup>7</sup>

Although their prevalence in humans is highly variable, *Actinomyces* are autochthonous oral cavity bacteria. The genus comprises several species of facultative anaerobic, gram-positive, branching rods, some of which are opportunistic endogenous pathogens. A broad spectrum of clinical manifestations accounts for the designation of “great masquerader”.<sup>8</sup> These include the classic “lumpy jaw syndrome” and other forms of chronic and acute suppurative infections, but, perhaps the most bizarre manifestation is its’ ability to present as an infiltrative slow growing lesion, mimicking advanced stage malignant neoplasia.<sup>9</sup>

As our knowledge regarding the interaction of the host’s immune system with the microbiome increases, researchers continue to find in bacteria the cause of previously considered idiopathic diseases. This is exemplified by *Helicobacter pylori*’s ability to induce chronic gastritis and mucosa-associated lymphoid tissue lymphoma.<sup>10</sup>

As illustrated by the present cases, the colonizing microbiome may have a role in oropharyngeal lymphoid hyperplasia. *Actinomyces* emerges as a possible etiological agent by its’ frequent association with tonsillar overgrowth and the ability to present as indolent infections resembling malignant lesions. In both cases no alternative causes for lymphoid hyperplasia were found, after extensive work-up. We believe this condition presents frequently as an incidentaloma, as occurred in the cases described.

Mucosal-bacteria interface represents a complex interaction ranging from coexistence without inflammation to invasion and infection. This dynamic equilibrium may be altered by individual inflammatory responses tailored to specific autochthonous species.<sup>11</sup>

## Conclusion

Commensal microbiome interaction with the immunologic system is complex and poorly understood. These cases, along with other reports in the literature, support a role for autochthon bacteria in chronic mucosal inflammation and subsequent reactive lymphoid hyperplasia, in selected patients. However, the role of oropharyngeal microflora is yet unclear, and more research is needed.



## Conflict of interest

None declared.

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