

## CASE REPORT

## Chronic Infectious Laryngitis: The Role of Empirical Therapy and Biopsy: A Report of 5 Cases

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### ABSTRACT

*Laringitis berjangkit kronik adalah mimik klinikal kanser peti suara disebabkan oleh etiologi bakteria dan kulat. Kedua-dua penyakit mempunyai gejala tidak spesifik dan leukoplakia semasa pemeriksaan. Peranan biopsi tanpa risiko kanser peti suara boleh dipertikaikan kerana ia biasanya responsif terhadap terapi antikulat. Kajian ini bertujuan untuk mengkaji faktor predisposisi dan peranan biopsi dalam laringitis berjangkit kronik. Semakan retrospektif terhadap kes laringitis berjangkit kronik di pusat kami antara 2018 dan 2021 telah dijalankan. Ciri-ciri klinikal, faktor risiko, terapi antikulat dan keberkesanan telah dikaji. Lima kes laringitis berjangkit kronik dirawat dengan jayanya dengan terapi antikulat empirikal kecuali satu kes refraktori. Biopsi kes refraktori adalah negatif untuk kanser dan *Staphylococcus aureus* laryngitis budaya telah berjaya dirawat dengan antibiotik. Terapi antikulat empirikal dalam kes laringitis kulat berjangkit kronik dengan susulan berkala mempunyai hasil yang baik. Biopsi harus dilakukan untuk kes refraktori untuk mengecualikan kanser dan membimbing terapi antimikrob selanjutnya.*

*Kata kunci: Biopsi; laringitis; serak; Staphylococcus*

### ABSTRACT

Chronic infectious laryngitis is a clinical mimic of laryngeal carcinoma which can be due to bacterial or fungal aetiology. Both conditions present with non-specific symptoms with leucoplakia on examination. The role of biopsy of laryngeal lesions in the absence of risk factors of laryngeal carcinoma is debatable as it responds to antifungal therapy. This study aimed to review the predisposing factors and

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role of biopsy in chronic infectious laryngitis. A retrospective review of all cases of chronic infectious laryngitis presented to our centre between 2018 and 2021 were conducted. Clinical features, risk factors, antifungal therapy and its response were reviewed. All cases of chronic infectious laryngitis avoided the need of biopsy while had successful empirical antifungal therapy except for one refractory case. Biopsy of the refractory case was negative for malignancy and the culture-proven *Staphylococcus aureus* laryngitis was successfully treated with antibiotics. Empirical antifungal therapy in cases of chronic infectious fungal laryngitis with close serial follow-up had good outcome. Biopsy should be reserved for refractory cases to exclude malignancy and guide further antimicrobial therapy.

Keywords: Biopsy; hoarseness; laryngitis; Staphylococcus

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## INTRODUCTION

Chronic laryngitis refers to the inflammation of larynx beyond three weeks and can be caused by infectious, inflammatory or autoimmune aetiologies. The incidence of chronic laryngitis is estimated to be 3.47 per 1000 population annually (Zhukhovitskaya & Verma 2019). Chronic infectious laryngitis can be due to bacterial or fungal infections. This condition commonly presents with non-specific symptoms of hoarseness (63-100%), odynophagia (9-19%), dysphagia (11-18%) and dyspnoea (18-19%) (Saraydaroglu et al. 2010; Shah & Klein 2012; Valente et al. 2020). In addition, laryngoscopy examination using video-endoscopy often shows leucoplakia or exophytic mass (Ibrahim & James et al. 2016; Saraydaroglu et al. 2010). This mimics laryngeal carcinoma which mandates further examination under anaesthesia and tissue biopsy for diagnosis. The biopsy has the potential risk of vocal fold scarring and irreversible alteration

to voice. Fortunately, majority of cases exhibited complete resolution with antimicrobial therapy (Carpenter & Kendall 2018; Valente et al. 2020). Hence, the role of biopsy and culture to establish diagnosis is debatable. We described a retrospective study of chronic infectious laryngitis that were successfully treated with empirical antimicrobial therapy except in one refractory case where biopsy and culture were performed to guide subsequent treatment.

## CASE REPORT

A retrospective review was conducted for all cases of chronic infectious laryngitis presented to Otorhinolaryngology clinic in our tertiary centre between 2018 and 2021. All patients included in this study had symptoms more than three weeks and were treated empirically with antifungal. Patients' presenting symptoms, comorbidities and videolaryngostroboscopy of the larynx were recorded. Laryngopharyngeal

reflux (LPR) was diagnosed based on a significant reflux symptom index (RSI  $\geq 13$ ) (Belafsky et al. 2002) and reflux finding score (RFS  $\geq 7$ ) (Belafsky et al. 2001). Response to treatment was determined by reduction of patients' symptoms and resolution of laryngeal lesions on video-laryngoscopy. Endolaryngeal microsurgery and biopsy were performed if no improvement was seen after one month of therapy.

### RESULTS

A total of five patients were identified (Table 1). Three were male and two were female. Age ranges from 40 to 62 years old. Two patients were active smokers. Two patients were on oral corticosteroid due to either category 5 COVID-19 pneumonia or systemic lupus erythematosus, two patients were on inhaled corticosteroid therapy for chronic inflammatory airway disease, and one patient had poorly controlled

diabetes mellitus. All patients presented with hoarseness ranging from one to two months, furthermore, two patients had voice fatigue, and one patient had sore throat. Three patients had significant RSI ranging from 13 to 21.

Video-endoscopy of larynx depicted varying degrees of leucoplakia over vocal folds only with oedema and surrounding erythema in all patients (Figure 1 to 4). One patient had granuloma over arytenoids while three patients had laryngeal features of LPR with RFS ranging from 7 to 14. Four patients underwent stroboscopy examination which demonstrated asymmetrical and aperiodic mucosal waves in all patients and incomplete glottal closure in two patients (Table 2). Chest radiography did not show any lesions in the lung fields and tuberculosis workup was negative for all patients. No oral thrust seen in oropharynx suggestive of oropharyngeal fungal infection.

TABLE 1: Demographic and comorbidities

Patient No.	Age (years)	Gender	Comorbidities	Steroid Usage	Tobacco Usage	Presence of LPR
1	50	Male	COVID-19 pneumonia, hypertension	High dose corticosteroid	Ex-smoker	No
2	47	Male	COPD	MDI fluticasone propionate	Active smoker	Yes
3	42	Male	-	-	Active Smoker	No
4	62	Female	Bronchial asthma, DM, hypertension, HF, OSA	DPI budesonide/ formoterol	Ex-smoker	No
5	40	Female	SLE	Oral prednisolone 30 mg OD	Non-smoker	Yes

COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HF: heart failure; LPR: Laryngopharyngeal reflux; OSA: obstructive sleep apnoea; SLE: systemic lupus erythematosus



FIGURE 1: Video-endoscope of larynx depicted leucoplakia at the anterior two-thirds of bilateral vocal folds



FIGURE 2: Video-endoscope of larynx depicted leucoplakia at the anterior one-third of right vocal folds with erythema over anterior two-thirds

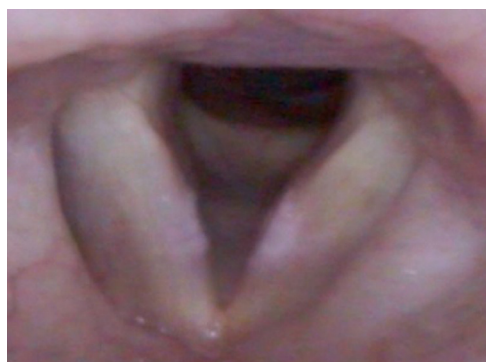


FIGURE 3: Video-endoscope of larynx depicted leucoplakia over the middle one-third of bilateral vocal folds with surrounding erythema

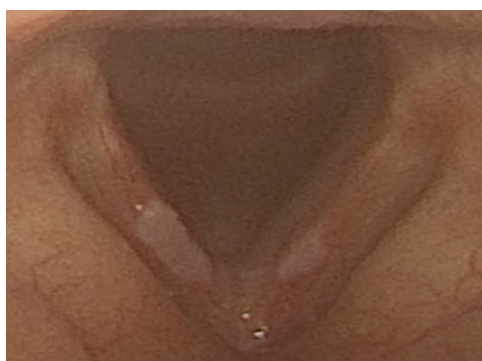


FIGURE 4: Video-endoscope of larynx depicted leucoplakia over the anterior one-third of bilateral vocal folds with surrounding erythema

All patients were empirically treated with either oral fluconazole 50-200 mg in once daily (OD) or twice daily dosing (BD) or itraconazole 100 mg BD (Table 2). Inhaled corticosteroid was discontinued in one patient while dry powder inhaler (DPI) was switched to metered-dose inhaler (MDI) in the other patient. Proton pump inhibitor (PPI) therapy was initiated for the patients with LPR.

All but one patient demonstrated complete resolution of laryngitis after a single course of antifungal therapy for three-six weeks. That patient had

worsening of symptoms and vocal fold condition despite one month of antifungal therapy. Endoscopic laryngeal microsurgery and biopsy under general anaesthesia were performed (Figure 5) and tissue culture grew *Staphylococcus aureus* which was sensitive to cloxacillin. Histopathological examination revealed acute on chronic inflammation with negative fungal stains. Oral cloxacillin 500mg four times a day was initiated with complete resolution was seen after six weeks.

TABLE 2: Symptoms, duration, stroboscopy examination during phonation and treatment

Patient No.	Symptoms	Duration of Symptoms (months)	Stroboscopy examination during phonation	Treatment
1	Hoarseness, voice fatigue	2	Severe asymmetrical and aperiodic mucosal waves, incomplete closure of glottis	Fluconazole 200mg BD x 6 weeks
2	Hoarseness	2	Mild mucosal wave asymmetry, reduced amplitude on the pathological side	Fluconazole 100mg OD x 3 weeks
3	Hoarseness	1	-	Itraconazole 100mg BD x 3 weeks
4	Hoarseness	2	Asymmetrical and aperiodic mucosal wave, reduced amplitude of vocal folds vibration	Fluconazole 50mg BD x 3 weeks
5	Hoarseness, voice fatigue, sore throat	2	Severe asymmetrical and aperiodic mucosal wave, incomplete closure of glottis, reduced amplitude of vocal folds vibration	Fluconazole 100mg OD x 4 weeks, then, cloxacillin 500mg QID x 6 weeks

BD: twice a day; OD: once daily; QID: four times a day

## DISCUSSION

Predisposing factors of chronic infectious laryngitis can be broadly categorised into factors altering systemic immune response and

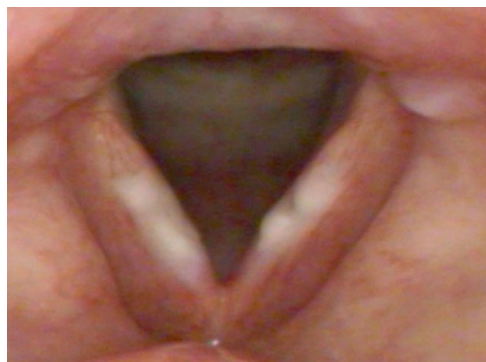


FIGURE 5: Video-endoscope of larynx depicting oedematous and erythematous bilateral vocal folds with leucoplakia seen at the edge of middle one-third bilaterally. A small granuloma was seen over the medial surface of bilateral arytenoids with subcordal oedema and posterior commissure hypertrophy

factors altering local mucosal barrier. Factors altering systemic immune response include immunosuppressive states such as uncontrolled diabetes mellitus or malignancies, and on immunosuppressive medications such as systemic steroids or chemotherapy (Mehanna et al. 2004). The differential diagnosis of chronic infectious laryngitis must be kept in mind in the cases presenting with hoarseness as most of the severe COVID-19 infection survivors are being discharged with long-term systemic steroids.

Factors affecting local mucosal barrier include previous radiotherapy, gastro-oesophageal reflux, inhaled corticosteroids, smoking, and trauma. (Mehanna et al. 2004) Inhaled corticosteroids usage has been implicated in 36-74% of the cases (Ibrahim & James 2018; Jeng et al. 2016; Saraydaroglu et al. 2010; Valente

et al. 2020). This is significant as inhaled corticosteroid is the mainstay of treatment in bronchial asthma and increasingly used in chronic obstructive pulmonary disease as combination therapy with long acting beta<sub>2</sub>-agonist as illustrated in our series. Smoking and gastroesophageal reflux were reported in 9-72% and 13-71% of cases, respectively (Carpenter & Kendall 2018; Ibrahim & James 2018; Jeng et al. 2016; Saraydaroglu et al. 2010; Valente et al. 2020).

Chronic fungal laryngitis is predominantly caused by *Candida albican*, while other uncommon organisms are *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans*, and *Paracoccidioides brasiliensis* (Mehanna et al. 2004; Zhukhovitskaya & Verma 2019). The commonest affected site is the glottic (45-98%) as illustrated in this case series (Ibrahim & James 2018; Valente et al. 2020). Laryngoscopy examination often reveals leucoplakia (18-50%), exophytic mass (39-54%), pseudomembrane (36%), mucosal oedema (30-44%) and mucosal erythema (33-38%) (Jeng et al. 2016; Saraydaroglu et al. 2010; Valente et al. 2020). Infection often occurs concurrently with oropharyngeal or pulmonary lesions (Mehanna et al. 2004). However, this is different in this case series, where all cases have isolated laryngeal lesions.

The mainstay of the treatment is antifungal therapy. Most authors reported the usage of oral fluconazole ranging from 100 to 400 mg OD for two to eight weeks with improvement

seen in 94-100% of patients (Ibrahim & James 2018; Jeng et al. 2016; Mesoellea et al. 2021; Valente et al. 2020). Duration of treatment is determined by clinical response to therapy. In addition, predisposing factors are managed accordingly. Lifestyle modification and PPI are initiated for gastro-oesophageal reflux and laryngopharyngeal reflux (Mehanna et al. 2004; Valente et al. 2020). Inhaled corticosteroids are withheld and controller inhaler medication changed to another class if feasible (Mesoellea et al. 2021). MDI is preferred over DPI as it has lower deposition in oropharyngolaryngeal airway (Ali et al. 2009). Diabetic control is optimised, and smoking cessation is advocated (Mehanna et al. 2004; Valente et al. 2020)

In the view of high response rate of chronic fungal laryngitis to antifungal therapy, the need of biopsy to establish the diagnosis is debatable. Empirical treatment with antifungal therapy can be initiated with close serial follow-up to assess response and monitor liver function. Biopsy should be performed for refractory cases to exclude any malignancy and guide further antimicrobial therapy (Carpenter & Kendall 2018; Jeng et al. 2016; Mesoellea et al. 2021; Sheth et al. 2022; Valente et al. 2020). Bearing in mind that biopsy carries the potential risk of vocal fold scarring and subsequently voice impairment, hence, biopsy should be performed judiciously with precision technique to avoid violating the vocal ligament. As illustrated in our case 5, there was clinical deterioration despite optimal therapy and biopsy of the larynx was performed, which revealed

Staphylococcal bacterial laryngitis. However, there is no consensus on the duration of empirical therapy before a biopsy is mandated. This is further complicated by the absence of specific laryngoscopic, stroboscopic or digital chromoendoscopic findings to reliably distinguish between chronic fungal laryngitis and laryngeal carcinoma.

Chronic bacterial laryngitis is commonly caused by *Staphylococcus aureus* with rising incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) (Shah & Klein 2012). Other organisms implicated are *Pseudomonas aeruginosa* and *Serratia marcescens* (Zhukhovitskaya & Verma 2019). Hallmark of chronic bacterial laryngitis on laryngoscopy examination are crusting, exudates, vocal folds erythema and oedema. Leucoplakia is occasionally seen (Carpenter & Kendall 2018; Shah & Klein 2012). Our case was atypical as there were no crusting or exudates seen which misled our initial diagnosis as fungal laryngitis in the presence of leucoplakia.

Treatment with antibiotics is often prolonged, requiring 6 to 9 weeks for resolution (Carpenter & Kendall 2018). This is similar in this case, where a total of 6 weeks of antibiotics was given based on serial endoscopy assessment of the larynx with antibiotics stopped upon resolution of symptoms and vocal fold lesions. Cloxacillin was chosen in this case based on the culture and sensitivity result. Other studies have suggested trimethoprim/sulfamethoxazole as the initial choice of empirical antibiotics against the possibility of MRSA infection (Carpenter & Kendall 2018).

## CONCLUSION

Chronic infectious laryngitis frequently presents with non-specific symptoms and often mimics carcinoma or premalignant lesion of the larynx. Hence, an index of suspicion must be maintained, especially in the current setting of COVID-19, where an increasing number of patients are being discharged with long-term corticosteroid therapy. Empirical antimicrobial therapy can be instituted along with close serial follow-up to assess response to therapy. Biopsy should be reserved for refractory cases to exclude malignancy and guide for further antimicrobial therapy.

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