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Laryngology

Magnetic resonance diagnosis of laryngeal chondritis after transoral laser microsurgery for laryngeal cancer

Risonanza magnetica nella diagnosi di condrite laringea post microchirurgia transorale laser per carcinoma della laringe

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SUMMARY

Objective. Laryngeal chondritis (LC) is a rare complication of carbon dioxide transoral laser microsurgery (CO_2 TOLMS) for laryngeal tumours and can pose a diagnostic challenge. Its magnetic resonance (MR) features have not been previously described. This study aims to characterise a cohort of patients who developed LC after CO_2 TOLMS and describe its clinical and MR findings.

Methods. Clinical records and MR images of all patients presenting with LC after CO_2 TOLMS between 2008 and 2022 were reviewed.

Results. Seven patients were analysed. Timing of LC diagnosis ranged from 1 to 8 months after CO_2 TOLMS. Four patients were symptomatic. Abnormal endoscopic findings included suspected tumour recurrence in 4 patients. MR documented focal or extensive signal changes involving the thyroid lamina and para-laryngeal space with T2 hyperintensity, T1 hypointensity and intense contrast enhancement (n = 7), and minimally reduced mean apparent diffusion coefficient (ADC) values (1.0-1.5 x 10^{-3} mm^2/s) (n = 6). A favourable clinical outcome was achieved in all patients.

Conclusions. LC after CO_2 TOLMS has a distinctive MR pattern. When tumour recurrence cannot be confidently excluded based on imaging, antibiotic therapy, close clinical and radiological follow-up and/or biopsy are recommended.

KEY WORDS: carbon dioxide transoral laser microsurgery, laryngeal tumours, laryngeal chondritis, head and neck imaging, magnetic resonance

RIASSUNTO

Obiettivo. *La condrite laringea (CL) è una rara complicanza della microchirurgia laringea transorale laser (CO_2 TOLMS) per neoplasie laringee e può rappresentare una difficile diagnosi. Le caratteristiche in risonanza magnetica (RM) della CL non sono state descritte. Questo studio vuole caratterizzare una coorte di pazienti che hanno sviluppato CL dopo CO_2 TOLMS e descriverne i rilievi clinici e RM.*

Metodi. *Le cartelle cliniche e le RM dei pazienti che hanno presentato CL dopo CO_2 TOLMS dal 2008 al 2022 sono stati rivisti.*

Risultati. *Sette pazienti sono stati analizzati. Il tempo di comparsa della CL variava da 1 a 8 mesi dopo CO_2 TOLMS. Quattro pazienti erano sintomatici. Rilievi endoscopici anomali hanno incluso la sospetta recidiva in 4 pazienti. La RM ha mostrato alterazioni di segnale focali o diffuse delle lamine tiroidee e dello spazio paralaringeo con iperintensità T2, ipointensità T1, intenso enhancement in 7 pazienti e ADC medio minimamente ridotto (1,0-1,5 x 10^{-3} mm^2/s) in 6 pazienti. Tutti i casi hanno avuto un decorso clinico favorevole.*

Conclusioni. *La CL dopo CO_2 TOLMS ha una pattern RM distintivo. Quando la recidiva neoplastica non può essere esclusa sulla base dell'imaging, si raccomandano terapia antibiotica, stretto follow-up clinico e radiologico e/o biopsia.*

PAROLE CHIAVE: *microchirurgia laringea transorale laser, neoplasie laringee, condrite laringea, imaging del testa-collo, risonanza magnetica*

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Introduction

Carbon dioxide transoral laser microsurgery (CO_2 TOLMS) [1] is an effective therapeutic option for the surgical treatment of selected laryngeal tumours, with high chances of local control, minimal functional impairment and low rates of procedure-related complications [2-6]. In detail, if the laryngeal tumour is clearly visualised and fully exposed under direct laryngoscopy [7,8], CO_2 TOLMS is suitable for laryngeal cancers ranging from T1 to selected T3 (T3 tumours due to invasion of the anterior paraglottic space or T3 tumours in patients unfit for open partial horizontal laryngectomy) [9,10]. The most frequently described late complications of such a surgical approach include aspiration pneumonia, vocal fold scarring, anterior commissure synechia and laryngeal granuloma [11-14]. Laryngeal chondritis (LC) is very rarely reported, with a maximum rate of 1% [12,15-17]. In our referral tertiary academic centre, a series of cases of LC following CO_2 TOLMS for laryngeal tumours were identified on follow-up by magnetic resonance (MR). Radiological and clinical differentiation from tumour recurrence proved to be challenging in most of these cases. Existing literature on this subject is scarce and, to our knowledge, the MR features of this complication have not been previously addressed. Therefore, this study aims to characterise a cohort of patients who developed LC following CO_2 TOLMS for laryngeal cancer, in order to raise awareness on this possible complication, and describe its clinical findings and key MR features.

Materials and methods

A retrospective search of clinical records and MR data of all patients presenting with LC as a complication of CO_2 TOLMS between 2008 and 2022, as registered in the head and neck database of University of Brescia, was carried out.

Clinical data

Baseline demographic and clinical data, surgical procedure description and clinical outcomes were retrieved from patients' records.

Surgical procedure

All patients were submitted to glottic or supraglottic CO_2 TOLMS. Types of resection were classified according to the European Laryngological Society (ELS) classifications for glottic [18] and supraglottic endoscopic resections [19]. Imaging follow-up at our center is performed with MR every 6 months during the first 2 years and annually thereafter. All patients were homogeneously followed by the same group of head and neck radiologists.

MR acquisition and image analysis

The following sequences were acquired in all patients: T2-weighted and T1-weighted sequences, diffusion-weighted imaging (DWI) and a volumetric T1-weighted gradient-echo sequence with fat saturation after contrast injection (VIBE). Motion-compensated sequences and dedicated surface coils were utilised [20]. MR images were reviewed in consensus by a fifth-year resident in Neuroradiology and an experienced head and neck radiologist.

Results

Patient cohort and clinical findings

A total of 7 patients (5 males, 2 females) were included in the present case series. Table I summarises the baseline and follow-up clinical characteristics of patients. Median age was 65 years (range, 58-78). Five patients were affected by glottic tumours and were submitted to CO_2 TOLMS cordectomy, while 2 were affected by supraglottic tumours and underwent CO_2 TOLMS supraglottic resections. Two patients were re-submitted to CO_2 TOLMS: patient No. 2 four months after the first procedure, due to tumour persistence, and patient No. 4 one month after the first resection, due to positive margins on histopathological examination. Regarding patients' history and comorbidities, one patient (No. 6) reported previous bilateral cordectomies (type I and type II) 13 years earlier for glottic tumours and was diagnosed with type 2 diabetes. Moreover, another patient (No. 4) had a previous diagnosis of thyroid carcinoma and underwent total thyroidectomy and cobalt therapy 40 years before. No other patients were submitted to any form of radiotherapy.

Timing of LC diagnosis ranged from 1 to 8 months (mean, 4) after CO_2 TOLMS. At diagnosis, 4 patients were symptomatic: patient No. 2 presented with dysphonia and effort-related dyspnoea, patient No. 5 with rapidly progressive dyspnoea, patient No. 6 with odynophagia and liquid dysphagia and patient No. 7 with dysphonia alone. The remaining 3 patients were asymptomatic.

Abnormal endoscopic findings were present in 6 patients: 4 patients presented endoscopic findings suspicious for tumour recurrence, while 2 presented glottic granulomas (one with a coexistent anterior commissure synechia).

Imaging findings

MR scans with findings of LC after CO_2 TOLMS were performed in the context of: further investigation of abnormal laryngoscopic findings in one asymptomatic patient (No. 1), further investigation in 4 symptomatic patients (No. 2, No. 5, No. 6 and No. 7), and routine follow-up in 2

Table I. Patients baseline and follow-up clinical characteristics and management.

Patient (No.)	Gender	Age (years)	Tumour site, histotype, and staging	Type of CO2 TOLMS	Timing of LC diagnosis	Clinical findings	Endoscopic findings	Management
1	Male	65	Supraglottic NEC T2N0M0	Type I supraglottic laryngectomy	4 months	Asymptomatic	Ipsilateral false vocal cord vegetative tissue and vocal cord hypomobility	Antibiotic therapy US-guided and transoral biopsies: inflammatory granulation tissue; no evidence of tumour Regular FU: MR at 1, 3, 6 and 9 (resolution) months
2	Female	75	Glottic SCC T1N0M0	Type II cordectomy (followed by a second Type Va cordectomy 4 months later)	2 months	Dysphonia and effort-related dyspnoea	Anterior commissure lesion with NBI pattern suspicious for tumour persistence	Antibiotic therapy US-guided biopsy: inflammatory granulation tissue; no evidence of tumour Regular FU: MR at 2 and 6 (resolution) months; laryngoscopy at 5 months
3	Male	58	Glottic SCC T2N0M0	Type Vcd cordectomy	3 months	Asymptomatic	Ipsilateral anterior-third vocal cord, anterior commissure and contralateral vocal cord lesions with NBI pattern suspicious for tumour persistence	Open partial horizontal (supracricoid) laryngectomy: no evidence of tumour
4	Male	72	Supraglottic SCC T3N0M0	Type IIIb supraglottic laryngectomy (followed by margin enlargement one month later)	8 months	Asymptomatic	Expected post-surgical findings	US-guided biopsy: inflammatory granulation tissue; no evidence of tumour Antibiotic therapy Regular FU: MR at 6, 8 and 11 (resolution) months; laryngoscopy at 6 and 8 months
5	Female	64	Glottic SCC T1N0M0	Type Vd cordectomy	1 month	Rapidly progressive dyspnoea	Irregular tissue thickening on ipsilateral vocal cord, anterior commissure and subglottis	Antibiotic therapy Transoral biopsies: inflammatory granulation tissue; no evidence of tumour Resolution at 6 months FU MR
6	Male	78	Recurrent glottic SCC T1aN0M0 (T1bN0M0 13 years before)	Type Vabcd cordectomy (followed by contralateral Type II cordectomy)	7 months	Odynophagia and liquid dysphagia	Anterior commissure synechia and small ipsilateral posterior vocal cord granuloma	Antibiotic therapy FU: MR at 2 and 6 (resolution) months
7	Male	58	Glottic SCC T1N0M0	Type Va cordectomy	6 months	Dysphonia	Ipsilateral vocal cord granuloma	Antibiotic and corticosteroid therapy Videolaryngoscopy-guided biopsy: inflammatory granulation tissue; no evidence of tumour Resolution at 2 months FU MR

CO_2 TOLMS: Carbon dioxide transoral laser microsurgery; FU: Follow-up; LC: Laryngeal chondritis; MR: Magnetic resonance; NBI: Narrow-band imaging; NEC: Neuroendocrine carcinoma; No.: number; SCC: Squamous cell carcinoma; US: Ultrasound.

asymptomatic patients (No. 3 and No. 4). The key MR findings encountered in these scans are summarised in Table II. All patients displayed signal changes involving the paraglottic space and thyroid lamina. High signal intensity on T2-weighted images (WI), low signal intensity on T1-WI and contrast-enhancement were present in all patients. T1-WI signal was hypointense compared to ossified cartilage, but it was slightly hyperintense compared to non-ossified cartilage (Fig. 1). The contrast-enhancement pattern was homogeneously intense in one patient, while 6 showed intense peripheral enhancement with less intense central enhancement (5 patients) (Figs. 1, 2) or central avascular components (1 patient) (Fig. 3). DWI documented minimally reduced mean apparent diffusion coefficient (ADC) values in 6 patients (mean ADC values ranging from 1.035 to 1.45 x 10^{-3} mm^2/s). Two main distribution patterns were distinguished: (1) focal thyroid chondritis/perichondritis (registered in 5 patients) and (2) extensive thyroid chondritis/perichondritis (registered in 2 patients). In the focal pattern group, full thickness focal cartilage erosion/involvement, lesion extension along the external surface of the thyroid lamina and deep laryngeal involvement adjacent to the inner surface of the thyroid cartilage were present in all 5 cases. In the extensive pattern group, major signal chang-

Table II. MR findings.

Feature	(n)
High signal on T2-WI	7/7
Low signal on T1-WI	7/7
Minimally reduced mean ADC values (1.04-1.45 x 10^{-3} mm^2/s)	6/7
Contrast enhancement	7/7
Homogeneous	1/7
Intense peripheral enhancement	6/7
Central avascular components	1/7
Focal full thickness thyroid cartilage erosion/involvement	5/7
Paraglottic space involvement	5/5
Lesion extension along external surface of thyroid lamina	5/5
Extensive full thickness thyroid cartilage erosion/involvement	2/7
Involvement of the cricoarytenoid unit	1/7

ADC: Apparent Diffusion Coefficient; MR: Magnetic resonance; WI: Weighted images.

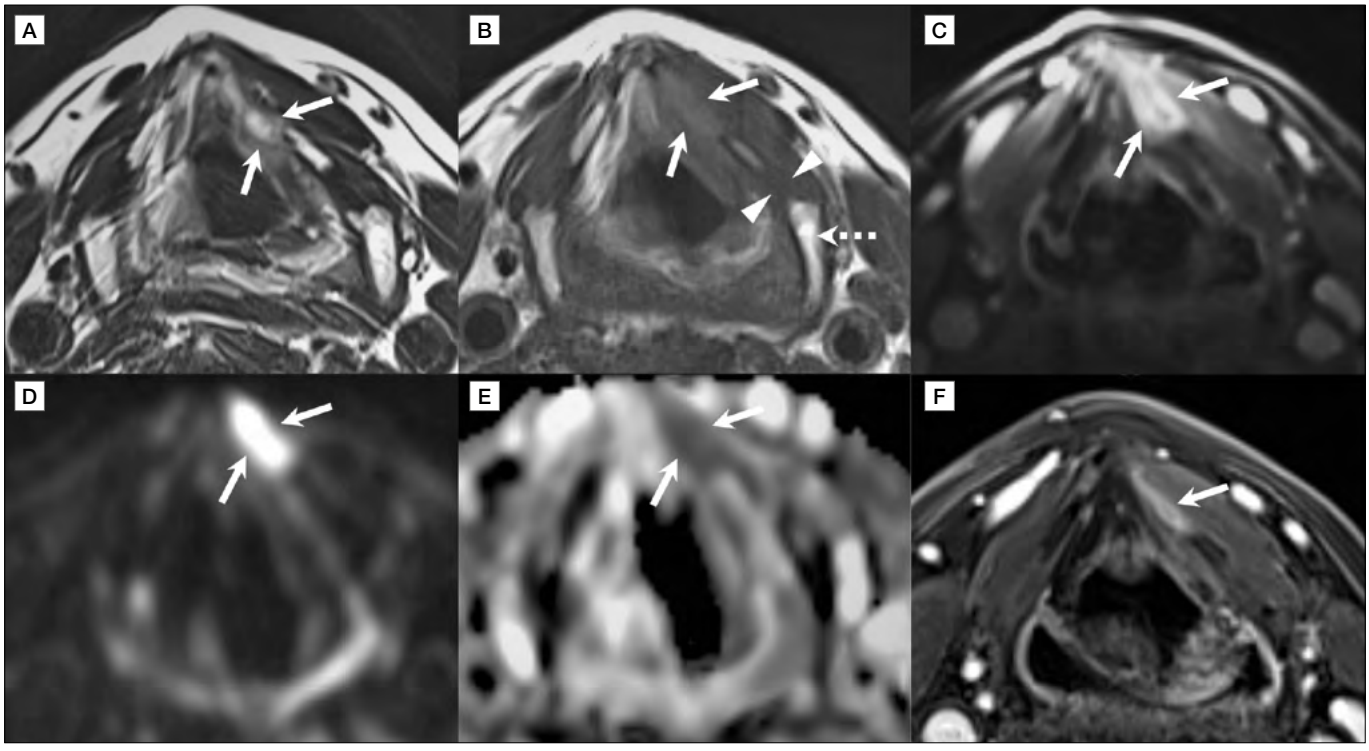

Figure 1. Focal post-CO_2 TOLMS LC in patient No. 6. Axial images at the supraglottic level: TSE T2-weighted (**A**), T1-weighted (**B**), contrast-enhanced fat-saturated T1 (VIBE) (**C**), DWI b900 (**D**) and ADC map (**E**). Focal lesion (arrows) involving the anterior residual left false vocal cord and the full thickness of the adjacent segment of the thyroid lamina. It is characterised by T2-weighted hyperintensity and T1-weighted hypointensity compared to ossified cartilage (dotted arrow in B), while it shows T1-weighted slightly hyperintense signal compared with non-ossified cartilage (arrowheads in B). There is intense peripheral contrast enhancement (arrows in C) and minimal diffusion restriction pattern (hyperintense signal on DWI and corresponding hypointense signal at the ADC map; mean ADC value of 1.2 x 10^{-3} mm^2/s). Axial contrast-enhanced fat-saturated T1 (VIBE) at 2 months follow-up (**F**) shows marked improvement of the LC process, with size reduction and decreased contrast enhancement of the focal lesion (arrow in F).

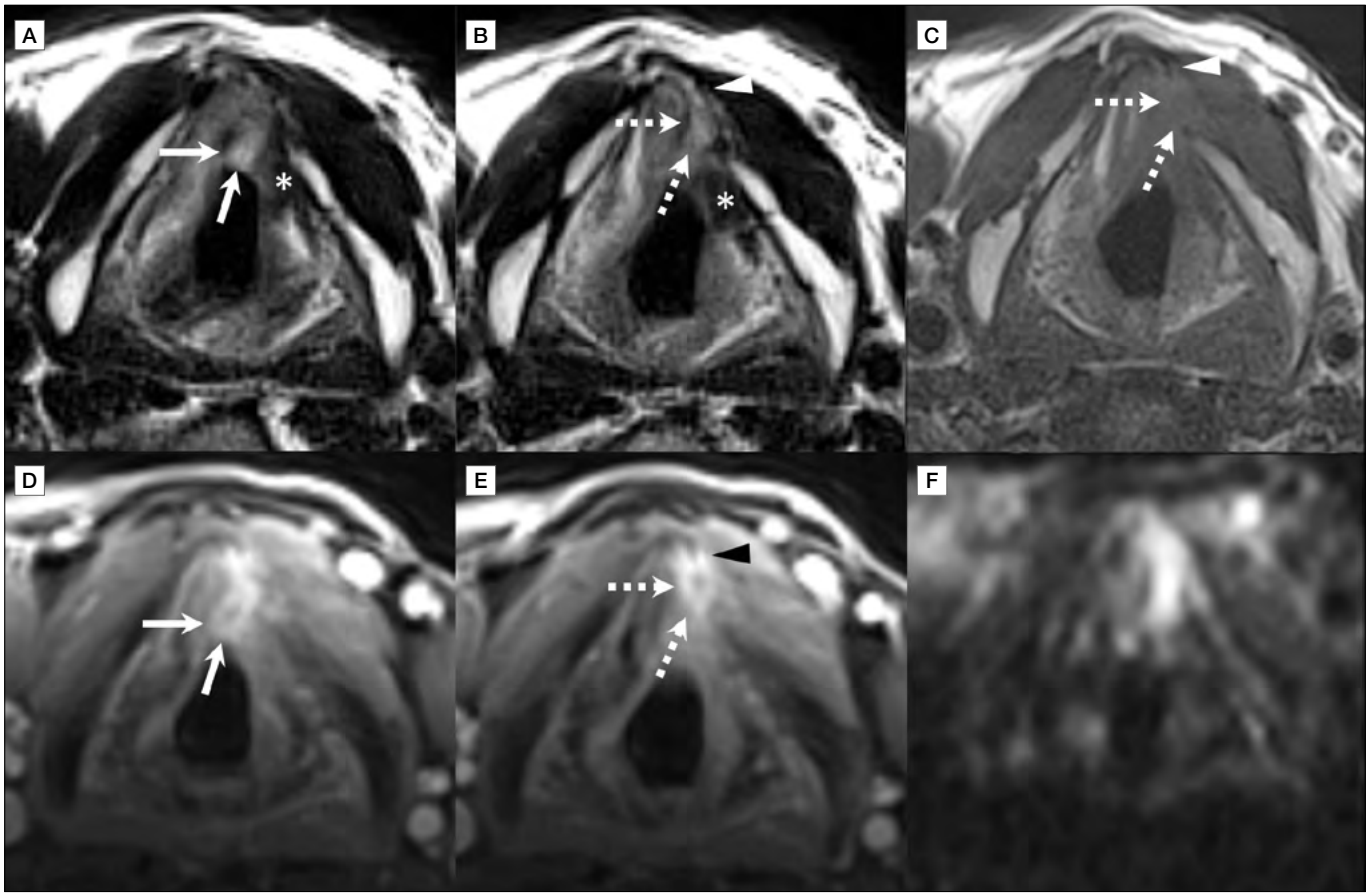

Figure 2. Focal post-CO_2 TOLMS LC in patient No. 3. Axial images at the glottic level (**A, D** and **F**) and immediately superior supraglottic level (**B, C** and **E**): T2-weighted (**A** and **B**), T1-weighted (**C**), contrast-enhanced fat-saturated T1 (VIBE) (**D** and **E**) and DWI b900 (**F**). Focal para-commissural lesion (arrows in A and D) at the residual left vocal cord, anterior to the T2 hypointense signal region of the cordectomy scar (asterisks in A and B). It extends deeply and involves the full thickness of the adjacent anterior thyroid lamina (dotted arrows in B, C and E). Notice slight extension along the external surface of the thyroid lamina anteriorly (arrowheads in B, C and E). This lesion shows slightly elevated T2-weighted signal, low T1-weighted signal, intense peripheral contrast enhancement and minimal diffusion restriction pattern (mean ADC value of 1.1 x 10^{-3} mm^2/s; ADC map not shown). While this lesion could be misdiagnosed as tumour recurrence, a biopsy confirmed post-CO_2 TOLMS thyroid chondritis.

es and swelling of the thyroid laminas were present. Patient No. 2 showed involvement of the superior two thirds of the laminae (Fig. 3), while in patient No. 5 both the entire laminae as well as the left cricoarytenoid unit were involved.

Management and follow-up

In the focal LC pattern group, MR findings were interpreted as a possible/probable inflammatory process in 2 patients and as probable tumour recurrence in another 2. In one patient, MR findings were initially interpreted as probable tumour recurrence, but were later re-considered as a possible inflammatory process. In 2 cases with an extensive LC pattern, MR findings were promptly recognised as chondritis. Clinical management and follow-up strategy are described in Table I. Antibiotic therapy was performed in 6 patients. Ultrasound (US)-guided transcutaneous, videolaryngoscopy-guided and/or transoral biopsies were performed in 5 patients, showing inflammatory granulation tissue and no evidence of tumour. One patient was submitted to open partial horizontal (supracricoid) laryngectomy and no signs of tumour recurrence were present at histopathological exam. Chondritis resolution was documented by follow-up MR in 6 patients (Figs. 4, 5). Time to resolution ranged from 2 to 11 months.

Discussion

The present paper describes a series of patients who developed inflammatory/infectious laryngeal complications – namely thyroid chondritis and perichondritis (an inflammatory process which may result in infection or necrosis) – after CO_2 TOLMS. Because such a complica-

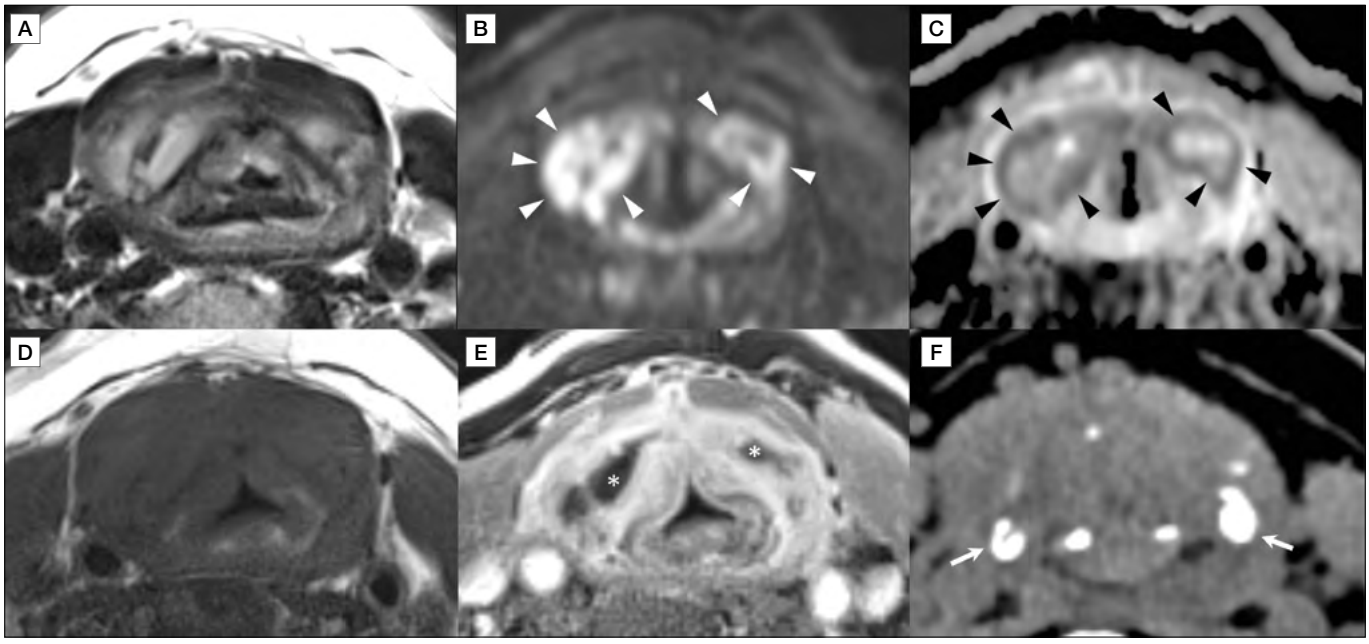

Figure 3. Extensive post-CO_2 TOLMS thyroid chondritis in patient No. 2. Different axial sequences at the level of the false vocal cords: T2-weighted (**A**), DWI b900 (**B**), ADC map (**C**), T1-weighted (**D**) and contrast-enhanced fat-saturated T1 (VIBE) (**E**), and soft-tissues window axial CT reconstruction at the glottic level (**F**). Swollen appearance and extensive full thickness signal changes of both thyroid laminae with very hyperintense T2-weighted and isointense T1-weighted signal, peripheral areas with diffusion restriction pattern, as demonstrated by high signal on DWI b900 and corresponding low signal on ADC map (arrowheads in B and C; mean ADC values of 1.05 x 10^{-3} mm^2/s), and intense peripheral contrast enhancement with central avascular areas (asterisks in E). Consequent reduction of the airway. On CT, there is extensive erosion of both thyroid laminae and only its most posterior segments are visible (arrows in F).

tion has not been previously addressed in the radiological literature, this setting poses a non-negligible clinical challenge. In detail, tumour recurrence was suspected in 2 MR exams and could not be confidently excluded in 3 cases. Therefore, the purpose of our work was to investigate these clinical pictures in order to acquire a better understanding of this complication and to identify its key imaging features, as well as trying to differentiate it from possible local tumour recurrence.

As reported in the literature, CO_2 TOLMS carries a relatively low risk of procedure-related complications [16]. These can be classified as intraoperative or post-operative (early or delayed) [12]. Post-surgical bleeding represents the most frequent intra- and/or early post-operative complication [5,16,21,22]. By contrast, the most commonly reported late complications include aspiration pneumonia (1.4%-11.5%) [11,12,16,21,22], vocal fold scarring with anterior glottic synechia (4.5%-10.6%) [2,13,14] and laryngeal granuloma (2%-10.6%) [13,14,23]. Although a potential risk for local infection is always present in any surgical intervention on the larynx, LC after CO_2 TOLMS is rarely described, with only a few series reporting rates ranging from 0.3% to 1% [12,15-17].

Inflammatory/infectious complications following CO_2 TOLMS and its risk factors have not been extensively reviewed in the literature. Despite the low rates reported, prophylactic measures are regularly applied and standard protocol at our institution includes prophylactic antibiotic therapy with ampicillin whenever thyroid cartilage has been extensively exposed or partially resected. Vilaseca-González and colleagues found that large tumour extension (cT3) and presence of diabetes was associated with higher complication rates, while no association was found with tumour site or patient's age [16]. In our series, only one patient had a relevant medical history of diabetes. Abouyared et al. reported an incidence of chondronecrosis of 23% after CO_2 TOLMS in a cohort of 52 patients previously submitted to radiotherapy [24]. However, the majority of these patients were submitted to CO_2 TOLMS within 5 years after radiotherapy. In our series, a single patient was previously submitted to radiotherapy 40 years before surgery. Regarding the type of resection, it is important to stress that all patients in our series submitted to glottic procedures underwent a type V cordectomy. It is conceivable that extensive cordectomies like these are associated with higher risk of inflammatory/infectious complications, particularly due to cartilage exposure and internal perichondrium removal. It is also plausible that patients re-submitted to CO_2 TOLMS, generally with broader resections, could face a higher risk of complication. In fact,

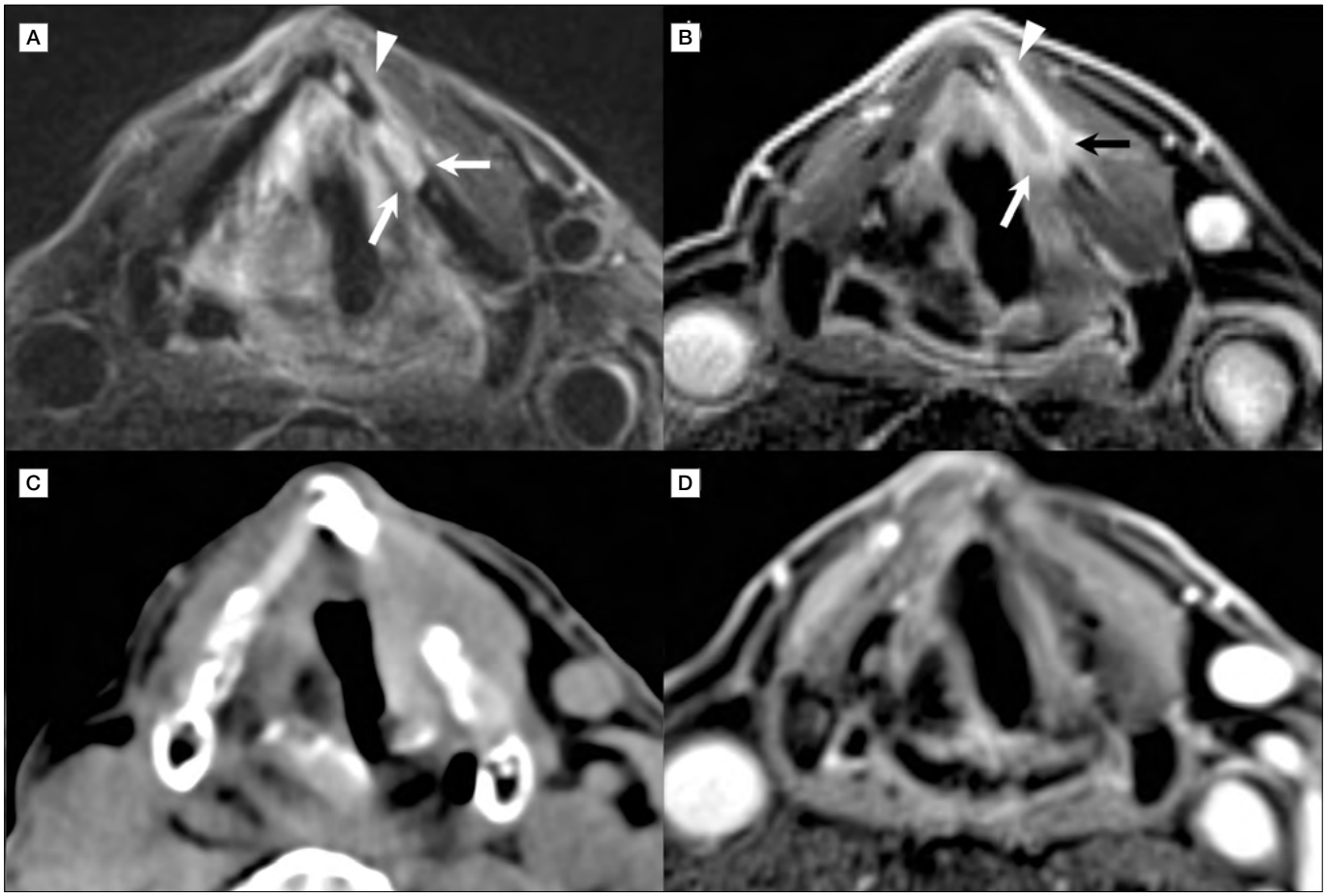

Figure 4. Focal post-CO_2 TOLMS LC in patient No. 4. Axial images at the glottic level: fat-saturated T2-weighted (**A**), contrast-enhanced fat-saturated T1 (VIBE) (**B**) and soft-tissues window CT reconstruction (**C**). Focal signal changes involving the full thickness of the left anterior thyroid lamina (arrows) with very hyperintense T2-weighted signal and intense peripheral contrast enhancement. Note the extension along the external perichondrial surface of the thyroid lamina anteriorly (arrowhead). On CT, focal full thickness erosion of the corresponding segment of the thyroid lamina is depicted (double-headed dashed arrow on C). Axial contrast-enhanced fat-saturated T1 (VIBE) (**D**) at 11 months follow-up shows complete resolution of the LC process, with no abnormal contrast enhancement areas.

3 patients in our series were re-submitted to laser surgery. Symptoms and clinical findings were unspecific or non-existent. Four symptomatic patients presented with rapidly progressive dyspnoea, effort-related dyspnoea, dysphonia, odynophagia and liquid dysphagia. Three patients were asymptomatic and, in these cases, LC was diagnosed during regular clinical (laryngoscopy) or radiological (MR) follow-up. Abnormal endoscopic findings were frequent but not suggestive of an infectious complication. Endoscopic findings suspicious for tumour recurrence were present in 4 cases (including 2 symptomatic patients). Laryngeal granulomas were found in 2 symptomatic patients (one patient also showing an anterior commissure synechia). In one asymptomatic case, no unexpected findings were registered.

We have previously described the expected imaging changes following CO_2 TOLMS, consisting of visualisation of volume loss and scar tissue within the surgical area, which is characteristically very hypointense on T2-WI with variable heterogenous contrast enhancement [20]. On the other hand, in the setting of post-CO_2 TOLMS LC we found a distinctive MR pattern characterised by soft tissue and thyroid lamina signal changes with high signal on T2-WI, low signal on T1-WI, minimally reduced mean ADC values and intense contrast-enhancement, most frequently intense peripheral enhancement. Focal and extensive chondritis/perichondritis patterns were registered. Cases with focal pattern consistently showed focal full thickness cartilage involvement and extension of the infectious process along the external margins of the thyroid laminae. This pattern proved to be the most challenging to diagnose, illustrating the importance of awareness on the possibility of post-CO_2 TOLMS LC and its key imaging features. Compared to LC, tumour persistence/local recurrence most often appears as

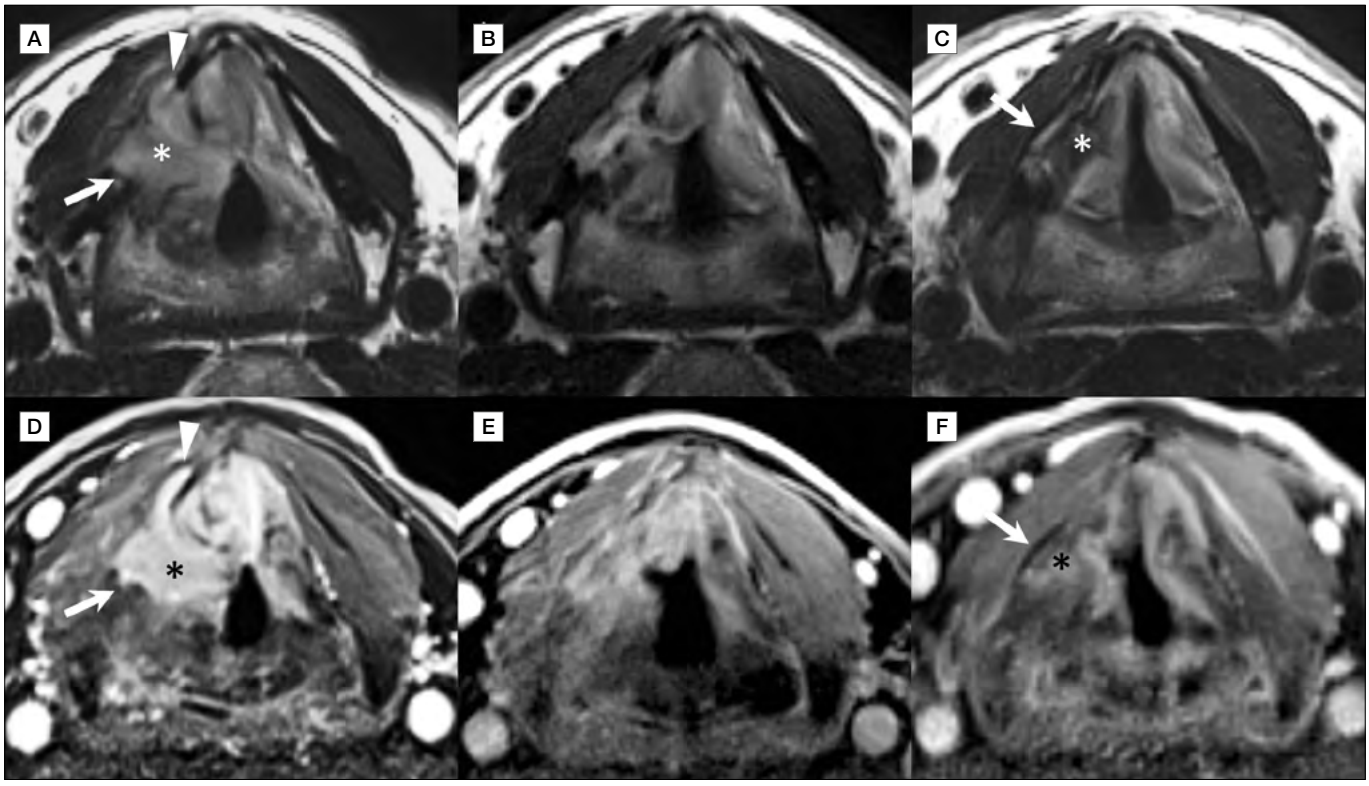

Figure 5. Chondritis evolution in patient No. 1. Axial T2-weighted (**A, B, C**) and contrast-enhanced fat-saturated T1 (VIBE) (**D, E, F**) images. Post-CO_2 TOLMS larynx MR (**A, D**) shows a lesion centred in the right paraglottic space deep to the middle and anterior thirds of the false vocal cord (asterisk) with bulging of the mucosa and consequent reduction of the airway. The lesion shows focal extension through the full thickness of the thyroid lamina (arrow) and along its external perichondral surface (arrowhead). It is characterized by T2-weigthed hyperintense signal and intense homogenous contrast enhancement. At one month follow-up (**B, E**), there was reduction of the extension of the lesion and decreased contrast enhancement. At 6 months follow-up (**C, F**), there was near-complete resolution of the LC process. An area of T2 low signal (scar tissue) with subtle contrast enhancement is now visible in the paraglottic space (asterisk) and the thyroid lamina appears as newly ossified (arrow).

a focal submucosal lesion with a lower (intermediate) T2-WI signal, diffusion restriction pattern on DWI and a diffuse, though less intense, contrast enhancement pattern [20]. On the other hand, cases with an extensive pattern showed near-total involvement of the thyroid laminae, which appeared diffusively swollen, and were promptly recognised as probable chondritis. The morphologic and signal changes mirror those witnessed in chondroradionecrosis, which are widely described in the literature and are therefore easier to interpret.

Despite the recognition of this distinctive MR pattern, our opinion is that confident exclusion of tumour recurrence, in most cases, is not possible based on imaging alone. In our series, all patients were submitted to close clinical and/or MR follow-up. Antibiotic therapy was administered in most patients (6 cases). Tumour recurrence was histopathologically excluded in 6 patients (following biopsy in 5 cases and open partial horizontal laryngectomy in one). US-guided transcutaneous biopsy is a widely accessible option and, according to our experience, seems to be safe and feasible in these patients. Resolution of MR changes was consistently registered, except in the patient submitted to open partial resection in which the extent of laryngeal framework compromise made it necessary to remove both thyroid laminae extensively involved by the LC process to avoid further airway complications. A favourable clinical outcome was achieved in all patients.

Limitations of the present study include its retrospective design and the paucity of the case series, which did not allow for appropriate statistical analysis.

Conclusions

LC is a rare but challenging complication of CO_2 TOLMS that laryngologists and radiologists should be aware of. Despite having unspecific clinical findings, it shows a distinctive MR pattern characterised by signal changes in cartilage and adjacent soft tissues with T2-WI hyperintensity, T1-WI hypointensity, minimally reduced mean ADC values and peripheral contrast enhancement. Focal or ex-

tensive patterns of LC can be documented. Dissemination of the inflammatory/infectious process along the external surface of the thyroid cartilage seems to be characteristic in the focal pattern; the extensive pattern resembles chondroradionecrosis. When tumour recurrence cannot be confidently excluded based on imaging alone, antibiotic therapy, close clinical and radiological follow-up and/or biopsy are recommended.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

BC: reviewed the subject, performed the literature search and clinical data analysis, collected, analyzed and reviewed the images, wrote and reviewed the manuscript; DL, AP, GZ, CP: collected and analyzed the clinical data and reviewed the manuscript; PR: helped writing and reviewed the manuscript; MR: conceptualized the manuscript, collected, analyzed and reviewed the images, helped writing and reviewed the manuscript; RM: conceptualized the manuscript and reviewed the images and the manuscript; IL: collected and reviewed the images; DF: reviewed the images and the manuscript.

Ethical consideration

This study was approved by the Clinical Research Ethical Committee of University of Brescia (protocol number NP4267). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Informed consent was waived.

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