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CASE REPORT

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Severe laryngeal edema after CAR-T cell treatment in a patient with multiple myeloma: A case report

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Key Clinical Message

This case aims to report an unusual clinical situation with uncommon and severe side effects, which can even be life threatening for the patient. The ENT and Hematology specialist should be aware of diagnosing and treating adequately.

KEYWORDS

adoptive immunotherapy, laryngeal edema, multiple myeloma

1 | CASE DESCRIPTION

1.1 | Clinical case

A 69-year-old male patient was seen in the ENT department of the Clinic University of Navarra in September 2019, presenting with an episode of sudden dyspnea and a drop in the oxygen saturation to below 70%. The patient had suffered from odynophagia in the previous days, associated with a pronounced dysphonia and a slight feeling of breathlessness. The patient was treated with corticotherapy and oxygen with nasal spectacles, with complete remission of the symptomatology. However, coinciding with the downward corticosteroid regimen, this previously mentioned symptomatology became progressively worse until triggering that episode of sudden dyspnea. A tracheostomy was finally needed to be carried out.

1.2 | Personal background

Initially, in March 2014, he had been diagnosed with lymphoplasmacytic lymphoma CD20+, and he started treatment with R-CHOP (x3) followed by three courses of R-bendamustine. In September 2014, after reviewing the diagnosis to an IgG kappa multiple myeloma, a second-line treatment was started with VTD (x4), achieving a *Very Good Partial Remission* (VGPR).

He started then third-line treatment in November 2016 with lenalidomide-dexamethasone, achieving adequate control of the disease.

Unfortunately, the disease progressed again in April 2018 with new lytic lesions on the CT scan. Fourth-line treatment with daratumumab-pomalidomide-dexamethasone was started on June 1, 2018. At the start of the cycle, he had BJ proteinuria 1432 mg/24 h urine collection, kappa chain 2047 mg/L.

He completed 8 cycles achieving VGPR as the best response. However, the disease progressed with the appearance of new bone lesions, highlighting one in C7 vertebrae, with involvement of the posterior arch, being in contact with the dural space.

He has received bridging therapy with radiotherapy in the lesions at C7, T8 and T10 on July. At that moment, he presented a performance status of ECOG 1 with absence of extramedullary disease in the physical examination.

In this situation, the patient was included in the B-cell maturation antigen CAR T-cell trial.

CAR-T (chimeric antigens receptor-T) cells therapy is a revolutionary therapy against hematological diseases. Its mechanism of action is based on the genetic modification of the patient's own T lymphocytes, so that they express receptors capable of recognizing the antigens present on tumor cells. Like any therapy, it is not exempt from complications. Among their main side effects, it could be mentioned: Cytokine Release Syndrome (CRS), by which a hyperinflammatory immune response is triggered after the infusion of CAR-T cells; the immune effector cell-associated neurotoxicity syndrome (ICANS), in which activation of immune cells causes toxicity at the central nervous system level; cytopenia-related adverse events, such as anemia, thrombocytopenia, leukopenia, and neutropenia;[1] an infusion reaction developed immediately after the infusion time; or a tumor lysis syndrome, due to lymphodepleting chemotherapy or direct destruction of malignant cells mediated by CAR-T cells,[2] among others.

Apheresis was performed in May 2019. An infusion was performed in August 2019.

1.3 | ENT physical examination, Evolution, and Therapeutic options

At the first consultation, endoscopic examination revealed severe edema of the arytenoid region, mainly dependent on the right side, which extended toward the anterior portion of the laryngeal vestibule, significantly compromising the airway, with preserved vocal cord mobility. The left vocal cord only showed slight edema (Figure 1). Given these findings and the initial improvement after oxygen therapy, a corticosteroid regimen (initial dose: 40 mg dexamethasone intravenous) was administered, showing after 2 h a significant decrease in edema. Both vocal cords, slightly swollen, could then be visualized appropriately.

As a diagnostic complement to the endoscopic examination, a neck/cavum CT scan was performed, which ruled out the presence of any mass and only showed the slight symmetrical soft tissue increase at the glottis level. Moreover, it showed the absence of the right arytenoid cartilage (Figure 2).

Analytically, the patient presented a D-dimer of 900 ng/mL and a ferritin of 837 ng/mL with a normal CRP. Likewise, he presented 2x10E9 leukocytes with 19.2% of lymphocytes and an elevated percentage of LTCD8+ (64.9%).

During the corticosteroid regimen, the patient did not present symptoms of dyspnea or dysphonia. However, a few days after decreasing the corticosteroid dose, he described a sensation of discomfort at the pharyngeal level and dysphonia, which the patient himself associated with treatment with inhaled pentamidine, which had been administered in the previous 48 h. The endoscopic examination carried out at that time showed a new slight increase in edema, especially at the level of the right arytenoid, which extends toward the left arytenoid, without edema in the vocal cords. No airway compromise was appreciated.

The need to maintain high doses of corticosteroids to control the edema and the lack of complete remission of the symptoms raised other treatment possibilities. In cooperation with the Allergology department, and given the possible diagnosis of angioedema, on suspicion of bradicinergic origin, an anti-bradicinergic therapy with icatibant 30 mg s/c was administered, showing a notable symptomatologic improvement 2 h after the treatment. However, this drug was losing its effect for hours, showing on endoscopic examination the persistence of edema, in this case, on the left arytenoid. In addition, before the administration of that drug, successive tests were carried out, showing in them levels of average inhibitor C1 concentration and normal function, as well as average C1q component value. Despite this, and given the lack of a precise diagnosis, it was decided to continue treatment with amchafibrin, although there was no apparent improvement. The levels of C4 in the first analysis were decreased, reaching typical values again during admission.

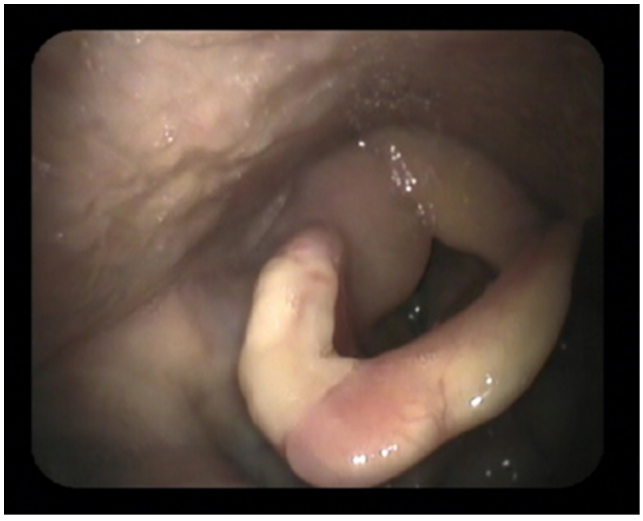

FIGURE 1 Severe edema of the arytenoid region.

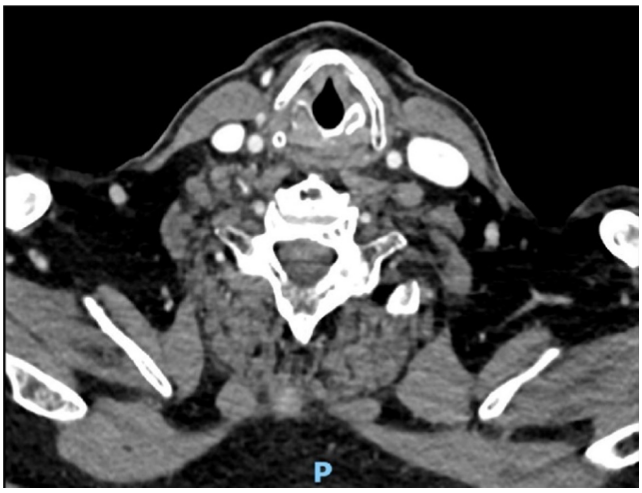

FIGURE 2 Neck/cavum CT scan showing the absence of the right arytenoid cartilage.

In the next 24 h, the patient presented a new episode of sudden dyspnea, so it was decided to carry out an emergency tracheostomy and take an epiglottis biopsy during the same surgical act. The pathological report concluded that it was angioedema, with no evidence of malignancy.

A daily endoscopic follow-up was then performed to document the patient's evolution.

1.4 | Clinical judgment

At first, within the main diagnostic possibilities, the following were considered: tumor lesion/infiltration, with mass effect, which compromised the airway (ruled out by CT scan and epiglottis biopsy) or angioedema, either in an allergic context or due to alteration in complement (C1 inhibitory deficit).

However, it is also important to highlight another antecedent of the patient. The medical team should probably have been given more consideration at the outset to better understand the symptomatology presented by the patient. Thus, in the 3 months before the onset of symptoms, the patient had received antalgic radiotherapy treatment on C7 and D10 vertebra and pubic lesion in another center, having prescribed a total of 20 Gy in 5 Gy fractions each in each volume one. After radiotherapy treatment, the patient reported having presented similar symptomatology, albeit subtler, consisting of odynophagia, slight dysphonia, and dysphagia, mainly for fluids. When analyzing the mean dose received, it was estimated that the mean dose received by arytenoids was 19.09Gy (minimum 18.50Gy and maximum 19.29Gy).

The evolution and response of the patient to the different therapeutic options administered, as well as the antecedent previously here mentioned, allowed us to consider as the principal diagnosis: Recurrent laryngeal edema, conditioning acute respiratory failure, finally attributed to recall effect in the context of inflammation and prior radiotherapy, in the context of IgG kappa multiple myeloma in 4° relapse, refractory to daratumumab-Pomdex (last line of therapy), following CAR-T infusion.

1.5 | Outcome and follow-up

Once the acute episode had been controlled, the patient was discharged with the tracheostomy cannula, indicating the steps to follow for its subsequent removal. He returned for a check-up at 2 months, referring to being asymptomatic, improving his voice, and with adequate tolerance to the covered tracheostomy tube 24 h a day. The videoendoscopic nasopharyngolaryngeal examination revealed a practically complete reduction of the edema located mainly in the arytenoid on the right side. As a result of the biopsy, the wound healing in the epiglottis was already complete at that time.

Given the favorable evolution presented by the patient, follow-up and decannulation were considered and suggested once he was in his usual place of residence.

On the other hand, and regarding the evolution of his underlying disease, a new lytic lesion in the sternum with a small extramedullary mass, not present in prior exams, was detected in May 2021 (last reevaluation in our center). In the blood test, positive immunofixation for free kappa light chains in the urine without Bence Jones's proteinuria and abnormal serum kappa free light chains (FLC kappa 25.7 mg/L; FLC Lambda 11.6 mg/L, ratio 2.22) with a standard ratio were found. Bone marrow evaluation shows <5% plasma cells, and MRD remains negative. This is compatible with a clinical relapse with one single lytic lesion.

Given the current situation and the fact that at this moment he has no measurable disease (only 25.7 mg/L of FLC), not qualifying then for inclusion in another clinical trial, it has been recommended to perform radiotherapy of the external lesions followed by maintenance with lenalidomide. Nonetheless, if the FLC would raise over 100 mg/L at any time, treatment in the context of clinical trials with new treatment modalities should be considered.

2 | DISCUSSION

The cause of the laryngeal edema presented by this patient remains to this day partially unknown.

The first cause considered was the extension of the underlying disease to the laryngeal or cervical level. However, this option was ruled out after performing the neck scan,

in which no mass was evidenced at this level, and it was later confirmed with the obtainment of the results of the epiglottis biopsy.

One of the hypotheses considered was the possibility of an adverse effect secondary to the infusion of CAR-T cells. This therapy has demonstrated unprecedented clinical responses when directed against CD19 in a variety of cancers, including acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), and chronic lymphocytic leukemia (CLL).[2] Moreover, this treatment is showing promising efficacy for the treatment of refractory multiple myeloma (RRMM) in multiple early-stage clinical trials.[1] Although serious adverse events and even deaths due to toxicity related to CAR-T cell therapy have been previously described, to date, there has not been evidenced recurrent laryngeal edema as a side effect attributed to this kind of treatment. The main adverse events presented in our patient after CAR-T infusion were: Grade 2 CRS treated with two doses of tocilizumab (day +3 and +5), Grade 2 ICANS, requiring transfer to the ICU on day +5, and being treated with steroids and levetiracetam, with rapid recovery and being discharged from ICU at day +8, and Grade 4 Aplasia, requiring transfusion support and G-CSF. During the hospitalization, the patient received eight pools of platelets, five packed red blood cells. As another possible main side effect, it could also have been considered the recurrent laryngeal edema. However, and as previously mentioned, it was finally attributed to recall effect in the context of inflammation and prior radiotherapy. Moreover, and in support of this conclusion, the development of laryngeal edema is widely known after the administration of radiotherapy at the cervical level, produced by inflammation and lymphatic alteration.[3–5] However, in most cases, this edema develops progressively and not as abruptly as we have seen in the clinical case presented here. Furthermore, after analyzing the radiation received by 66 patients diagnosed with squamous carcinoma of the head and neck, Sanguineti G. et al. concluded that the mean dose of Gy received at the laryngeal level required for the development of edema is ≥50Gy.[6] Our patient only received an estimated total of 20Gy in the glottic region, so a priori, radiotherapy treatment could not explain, in isolation, all the symptoms experienced by our patient.

A predictive tool for oncologic response to treatment is ^{18}F-FDG-PET imaging technique. However, this is a test with low specificity, since inflammatory changes due to treatment itself, benign infectious processes and even sterile inflammatory processes can cause focal uptake of the radiopharmaceutical.[7] For this reason, when recall radiation is suspected, FDG-PET would have been a useful tool to diagnose a severe inflammatory process, even though another diagnostic test would have been necessary to rule out the existence of a focal oncologic invasion.

3 | CONCLUSIONS

Any alteration in the airway can pose great risks to the patients, even threatening their life. A proper and a rapid management, in collaboration with other specialists, as well as a complete review of the medical history of the patient, will allow reaching accurate diagnostic conclusions, in order to establish the best available treatment option.

On the other hand, this recurrent laryngeal edema finding is especially relevant when it comes to monitoring patients who have received radiotherapy and who are being treated with CAR-T cells. Nasofibroendoscopy is an easy and safe procedure and its implementation in the follow-up of these patients could be considered highly recommended in any suspicious case.

AUTHOR CONTRIBUTIONS

Marta Alvarez de Linera Alperi: Conceptualization; writing – original draft. **Sol Ferran:** Writing – review and editing. **Maria Luisa Palacios Berraquero:** Investigation. **David Terrasa Czapiewska:** Writing – review and editing. **Ana Alfonso:** Supervision; writing – review and editing. **Secundino Fernandez:** Conceptualization; resources; supervision; validation; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no possible conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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