local subcutaneous soft tissues. The area of complete wound repair reached more than 90% in most patients we treated. Even if small scars or slight depression were left, the patients were satisfied on the whole. Compared with flap transfer and other methods, the method of local regeneration repair treats for small defects of skin soft tissues on the nasal sidewall, does not increase any extra incision, decreases the economic burden, and reduces the medical risk and technical difficulty. What is more, its repair effect is better, so this method is worthy of clinical promotion.

Due to the relatively small number of cases in this group, there are some limitations in this study:

(1) The size of wounds that cannot heal completely cannot be accurately evaluated, because we has not obtained the medical records that the wounds size larger than 10 mm;
(2) as for the small defects of skin and soft tissues at the junction of perioral, eyebrow, and other organs, it needs further clinical verification;
(3) mostly young and middle-aged, healthy patients in this group have strong ability of tissue healing.

Therefore, whether it is suitable for the elderly with weak healing ability or not, which needs further clinical research. And for those with chronic diseases such as diabetes and hypertension, it also needs further clinical verification. We believe that with the continuous progress of stem cells, regenerative medicine, and tissue engineering, the speed and quality of tissue regeneration will be further improved, which will provide theoretical and practical support for repair of tissue defects by tissue regeneration in situ.

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Differential Diagnosis of Negative Pressure Pulmonary Edema During COVID-19 Pandemic

Irem Karaman, MS and Sevket Ozkaya, MD†*

Abstract: Negative pressure pulmonary edema (NPPE) is a form of noncardiogenic pulmonary edema that typically occurs in response to an upper airway obstruction, where patients generate high negative intrathoracic pressures, leading to a pulmonary edema especially in the postoperative period. Here, we report a case of NPPE following general anesthesia that can easily be misdiagnosed as COVID-19 both radiologically and clinically during this pandemic. Twenty-year-old male was presented with sudden onset respiratory distress, tachypnea, and cyanosis just after the rhinoplasty surgery under general anesthesia. Chest radiography and thoracic computed tomography scans revealed the bilateral patchy alveolar opacities with decreased vascular clarity that looks similar to COVID-19 radiology. Negative pressure pulmonary edema is a sudden onset and life-threatening complication following general anesthesia particularly after head and neck surgery in young healthy individuals. It is a clinical condition that cannot be diagnosed unless it comes to mind. While both NPPE and COVID-19 cause hypoxemia and respiratory distress, as well as ground-glass opacities in the chest computed tomography, those opacities in NPPE appear mostly in central areas, whereas those opacities are mostly seen in peripheral areas in COVID-19. Furthermore, while NPPE cause decreased vascular clarity, COVID-19 causes vascular dilatations in the areas of opacities. Those differences together with medical history of the patient is crucial to differentiate these 2 similar identities. Negative pressure pulmonary edema requires an immediate recognition and intervention, therefore, we would like to raise the awareness of clinicians for such condition to avoid possible mistakes during the pandemic situation.

Key Words: COVID-19, negative pressure pulmonary edema, noncardiogenic pulmonary edema

Negative pressure pulmonary edema (NPPE) is a sudden onset and life-threatening complication following general anesthesia in young healthy adults. It is defined as a form of noncardiogenic pulmonary edema (NCPE) that results from the generation of high negative intrathoracic pressure following forced spontaneous

From the *School of Medicine, Bahcesehir University; and †Department of Pulmonary Medicine, Faculty of Medicine, Bahcesehir University, Istanbul, Turkey.
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Address correspondence and reprint requests to Sevket Ozkaya, MD, Associate Professor, Department of Pulmonary Medicine, Faculty of Medicine, Bahcesehir University, Sahrayi Cedit Mahallesi, Batman Sk. No:66, 34734 Kadiköy/Istanbul, Turkey;
E-mail: ozkayasevket@yahoo.com
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breathing against upper airway obstruction after nasal or upper airway surgery.[1] It is reported that NPPE is seen in 0.1% of cases with general anesthesia requiring tracheal intubation, with post-anesthetic laryngospasm is reported to be the reason in more than half of the cases.[2] Other causes of NPPE include foreign body aspiration, hematoma, smoking, obesity, delayed recovery from general anesthesia, obstructive sleep apnea syndrome, and oral and maxillofacial surgeries.[3] Postanesthetic NPPE occurs more frequently than it is documented in studies, and it can easily be missed or misdiagnosed when it is not taking into consideration among differential diagnosis. Current literature suggests that in cases of unexplained postoperative pulmonary edema, NPPE should be among the first things to be remembered.[2]

Given the overwhelming number of cases of coronavirus disease (COVID-19) patients, clinicians have struggled to distinguish the non-COVID-19 patients who required special attention other than giving COVID-19 treatment.[4] Due to the similarities in clinical features between 2 entities, such as hypoxemia, radiographic ground-glass opacities and altered lung compliance, and as NPPE is rarely seen, development of respiratory distress and low oxygen saturation in the early-postoperative period might easily be misdiagnosed as COVID-19 in the current pandemic situation.[3–5] Here, we report a case of NPPE that can easily be misdiagnosed as COVID-19 and we would like to help clinicians to promptly recognize and differentiate this serious complication from COVID-19.

CASE PRESENTATION

A 20 years-old male was consulted to the pulmonary department for development of acute respiratory failure after an elective rhinoplasty surgery by otorhinolaryngology clinic. His medical history was not remarkable. His posterioranterior chest X-ray, Electrocardiography (ECG), biochemical laboratory tests, and physical examination were within the normal limits before the surgery. He was classified with American Society of Anesthesiologists physical status I without a history of cardiorespiratory disease, gastroesophageal reflux, medicine, or surgeries. General anesthesia was induced with fentanyl, propofol, and vecuronium intravenously. The patient's trachea was intubated with cuffed endotracheal tube of size 7.0 mm. Anaesthesia was maintained with isoflurane and vecuronium bromide.

During the rhinoplasty procedure, his intraoperative oxygenation and lung mechanics were within the normal limits and the surgery went uneventfully. Postoperatively, the patient arrived to the recovery room breathing spontaneously and initially had no problems. Shortly thereafter in the recovery room, he became agitated, with evidence of total airway occlusion and negative inspiratory effort lasting several minutes, associated with tachycardia, increased respiratory rate, cyanosis, and hypoxemia. A pulmonologist was urgently consulted. 100% O_2 delivery was started with an anatomical face mask in the observation room. On auscultation, there were fine crepitations in most of the lung zones.

His supine post-op chest radiography showed diffuse bilateral pulmonary edema with mixed increased alveolar and interstitial infiltrates, interlobular thickening together with evident air bronchograms and an increased cardiothoracic ratio (Fig. 1A). His post-operative ECG and cardiac examination revealed no abnormal findings. A primary diagnosis of negative pulmonary pressure edema was made with regards to patient's operation history, clinical features, and differential radiological images. He was started to receive 100% O_2 with nasal cannula and diuresis treatment with furosemide for 24 hours and a chest x-ray revealed partially increased ventilation of the lung with persistent alveola-reticular linings at the end of 24th hour (Fig. 1B). Then, Thorax computed tomography was performed for the concern of COVID-19 due to current pandemic. Thoracic computed tomography scans revealed

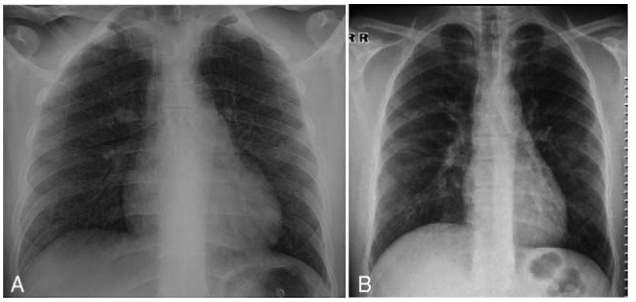

FIGURE 1. (A) His supine post-op chest x-ray showed diffuse bilateral pulmonary edema with mixed increased alveolar and interstitial infiltrates and interlobular thickening together with evident air bronchograms and an increased cardiothoracic ratio. (B) Chest x-ray of the patient 24 hours after diuretic therapy. In this graph, lung ventilation seemed partially increased, however, alveolar-reticular prominence was still observed.

the bilateral central patchy alveolar opacities representing pulmonary edema with decreased vascular clarity in the upper and lower lobes of the lung (Figs. 2 and 3). After 24 hours in the service, his vitals turned within the normal limits. He was discharged in post-op day 2 with a control appointment scheduled for 1 week later. After 1 week, his chest x-ray revealed resolved diffuse bilateral pulmonary edema (Fig. 4).

DISCUSSION

Negative pressure pulmonary edema is a form of NCPE that results from the generation of high negative intrathoracic pressure needed to overcome a possible upper airway obstruction.[5] The hydrostatic forces in the intact alveolar epithelium are blamed to be the primary mechanism behind acute post-obstructive pulmonary edema. This rare but dangerous complication was first hypothesized in 1927 by Morre but was first described by Oswalt in 1977.[6] Since then, numerous reports cases of NPPE related to general anesthesia following the head and neck surgery have been published.[1,3,7–9]

Acute onset perioperative pulmonary edema might have both cardiac and noncardiac causes. The diagnosis of cardiogenic pulmonary edema is confirmed with apparent cardiac symptoms with consistent ECG findings and elevated pro-Brain natriuretic peptide

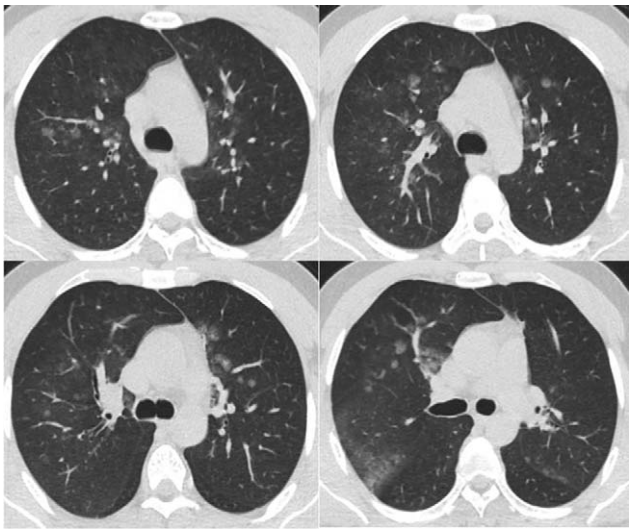

FIGURE 2. Thoracic High-resolution computed tomography images after 24 hours of diuretic treatment revealed the bilateral patchy ground-glass opacities and consolidations in the central areas of upper lung lobes.

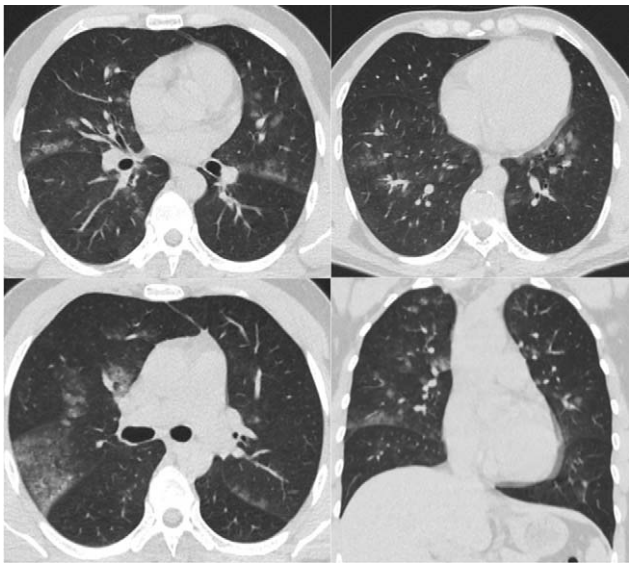

FIGURE 3. Thoracic High-resolution computed tomography images after 24 hours of diuretic treatment demonstrated central and partially peripherally located bilateral alveolar ground-glass opacities in the lower lung lobes that look similar to COVID-19 radiology.

and cardiac enzyme levels. On the other side, evidence of acute airway obstruction in the absence of other clinical symptoms such as normal biochemical and cardiac parameters with consistent radiological chest x-ray findings confirm the non-cardiogenic NNPE diagnosis.[7] Differential diagnosis of NNPE based on the initiating mechanisms of pulmonary edema includes lymphatic insufficiencies, impaired starling forces, altered alveolar capillary membrane permeability as seen in acute respiratory distress syndrome and postoperative NNPE. The existence of acute airway obstruction is the most important finding distinguishing the diagnosis of NNPE from acute respiratory distress syndrome postoperatively.[7]

FIGURE 4. After 1 week, chest x-ray showed resolved diffuse bilateral pulmonary edema.

The occurrence of NCPE has been observed after a variety of inciting events, including NPPE, neurogenic pulmonary edema, iatrogenic fluid overload, anaphylaxis, and acute lung injury.[7] Both the diagnosis of pulmonary edema and an understanding of its underlying pathophysiology have important implications for its treatment.[8] For this reason, the first step of diagnosis of NPPE should be to kept in mind of this clinic condition during the perioperative period. It should be noted that sudden onset respiratory failure and bilateral patchy infiltrates are the most common findings of NPPE.[2] The fact that the COVID-19 being among the differential diagnosis separates our case from prior reports. While both NPPE and COVID-19 cause ground-glass opacities in the chest CT, those opacities in NPPE appear mostly in central areas, whereas those opacities are mostly seen in peripheral areas in COVID-19. Furthermore, while NPPE cause decreased vascular clarity, COVID-19 causes vascular dilatations in the areas of opacities.[2,4,7] Those differences together with medical history of the patient is crucial to differentiate these 2 similar identities.

Although many patients with NPPE recover with conservative management, some patients with severe NPPE may require temporary intubation and mechanical ventilation with positive end-expiratory pressure.[8,9] Diuretics such as furosemide use is controversial and should be considered on patient basis, but it is often administered, as in our case. Negative pressure pulmonary edema is generally a benign condition typically resulting in full recovery in 12 to 48 hours when recognized early and necessary supportive treatment is instituted for hypoxemic and/or hypercapnic respiratory failure.[8,9] Currently, there is no intervention proven to prevent NPPE.[9]

In conclusion; NPPE is a rare but serious complication following general anesthesia that requires immediate intervention and close follow-up. It is a clinical condition that cannot be diagnosed unless it comes to mind. Diagnosis and treatment of NPPE requires a multidisciplinary approach, therefore a detailed medical history must be taken into consideration when evaluating the radiological and clinical features of the patient. All clinicians must be aware of the differences between 2 similar conditions, COVID-19 and NPPE, to avoid possible mistakes.

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