Case Series

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Histopathologic Findings of Olfactory Mucosa in COVID-19 Patients

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Abstract

Background: Olfactory manifestations are common findings during the course of COVID-19, while exact physiopathology is not known

Aim: We review histological changes of the nasal olfactory mucosa in COVID-19 non-survivors who died in the ICU.

Methods: Sampling was done within 1 hour of death under direct vision. Specimens were taken medial to the middle turbinate in the cribriform area, embedded in paraffin blocks, and stained by haematoxylin and eosin.

Results: The most frequent histologic finding was the infiltration of inflammatory cells mostly comprised of lymphocytes. Inflammatory infiltration of mucosa was seen in all 11 patients with ulceration in 9 cases and neuritis in 3 cases.

Conclusion: Inflammatory infiltration of olfactory mucosa may be associated with smell manifestations. Further histological studies will clarify the role of the nasal mucosa in the physiopathology of COVID-19 especially olfactory involvement.

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Introduction

Anosmia or hyposmia are common symptoms in COVID-19 patients but definite physiopathology underlying of olfactory dysfunction in these patients is unknown (1). Direct microscopic examination of olfactory mucosa may be a valuable method to discover cellular changes associated with olfactory symptoms. We designed the study to evaluate histological changes of the nasal olfactory mucosa in COVID-19 non-survivors admitted to the intensive care unit (ICU).

Methods

We performed this study from April 1 to May 1, 2020, in a tertiary hospital in Tehran. Informed consent was received from relatives of non-survivors and the proposal of the study was approved by the Institutional Research Ethics Committee, Shahid Beheshti University of Medical Sciences (approval ID was: IR.SBMU.NRITLD.REC.1399.069). Adult patients with real-time polymerase chain reaction (PCR) proven COVID-19 diagnosis admitted to ICU died because of the disease

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entered the study. Sampling was done within 1 hour of death under direct vision of a 0-degree, 4 mm diameter endoscope, with cutting forcepses. Bilateral mucosal specimens were taken medially to the middle turbinate in the cribriform area. All samples were immediately fixed in 10% formalin solution and were sent for histologic studies. Clinical and demographic information of patients gathered from ICU recordings.

Results

We performed sampling in eleven patients, 8 males and 3 females died in the ICU. Except for case no.6, all patients were older than 50, ranging from 37 to 89. Except for smell complaints in cases no.5 and no.6, there were no specific data about rhinologic symptoms. Clinical data of patients are presented in Table 1.

Table 1. Demographic characteristics of 11 ICU admitted coronavirus patients.

Cases	Age	Gender	Co-morbidity	Duration of symptoms to Admission(days)	Duration of Admission(days)	Duration of ICU Admission(days)	Cause of Death
1	66	M	HTN	7	8	8	ARDS
2	89	M	COPD	7	9	6	ARDS
3	75	F	HTN, Nephropathy	3	12	9	ARDS
4	66	M	HTN. IHD	22	19	7	ARDS, PTE
5	63	F	HTN. DM. IHD	8	5	5	ARDS
6	37	M	-	10	6	6	ARDS
7	63	M	Heart Failure	7	18	13	ARDS, Myocarditis
8	66	F	DM. HTN	24	3	1	ARDS, MI
9	50	M	DM	6	6	6	ARDS
10	53	M	DM	10	8	1	ARDS
11	87	M	DM	8	8	4	ARDS

HTN: hypertension, COPD: chronic obstructive pulmonary disease, IHD: ischemic heart disease, DM: diabetes mellitus, ARDS: acute respiratory distress syndrome, PTE: pulmonary thromboembolism, MI: myocardial infarction

Histopathologic Findings

Twenty-two autopsy specimens were received from 11 patients in formalin, including right and left nasal mucosal samples. All specimens were submitted and embedded in paraffin blocks. At least 2 sections were provided from each paraffin block. All sections were stained by hematoxylin and eosin. In selected specimens, immunohistochemistry for leukocyte common antigen (LCA) was done to highlight inflammation (Figure 1). The most frequent histologic finding in all nasal samples was the infiltration of inflammatory cells, mostly comprised of lymphocytes, including 2 patients with heavy inflammatory cell infiltration. Nine patients showed deposition of fibrin-leukocytic exudate and mucosal ulceration. In 6 patients variable numbers of budding yeasts and pseudo-hypha were seen in favor of candida colonization. Three patients showed sub-epithelial stromal hyalinization, and 3 cases revealed infiltration of nerve fibers by inflammatory cells. Other individuals had no included nerve fibers. In two patients, squamous metaplasia and reactive changes of surface epithelial cells were evident. Two patients revealed foci of mucosal necrosis, and small to medium-sized vessel thrombus formation was seen in 1 patient (Table 2).

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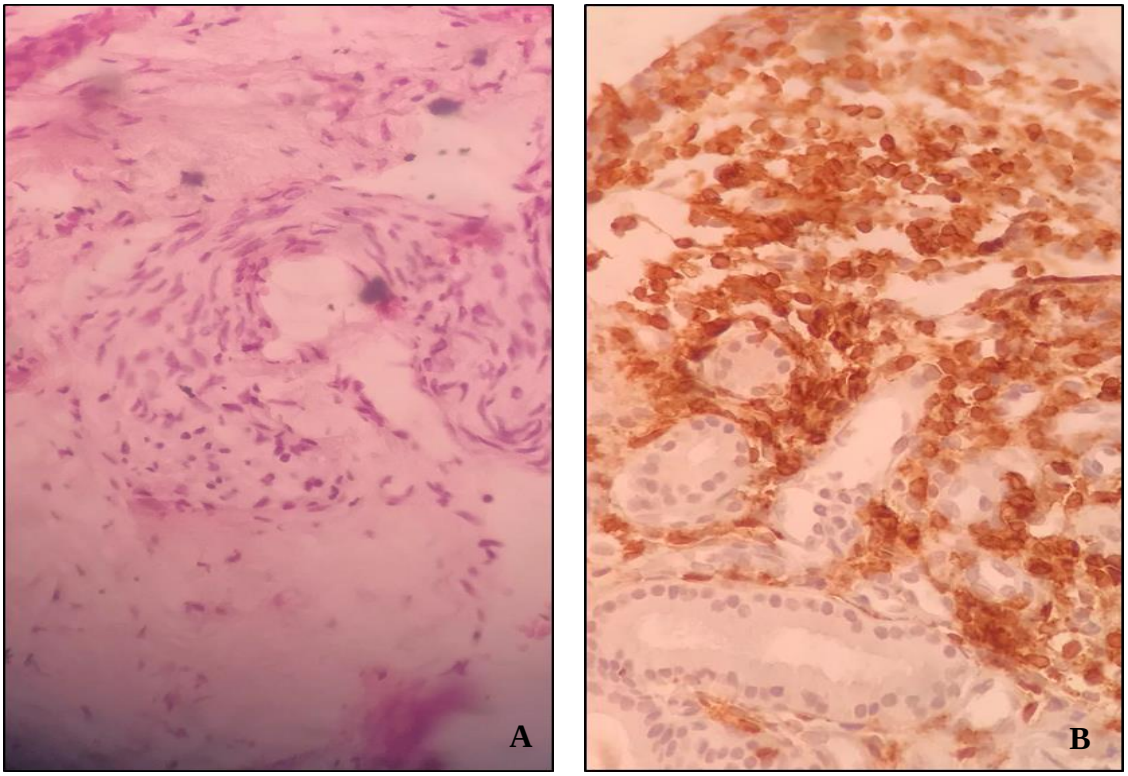

Figure 1. Histologic findings of nasal mucosa. Figure 1A: Infiltration of olfactory mucosa with lymphocytes. Figure1B: Immunohistochemistry stain with CD45

Table 2. Histologic findings of eleven non-survived coronavirus patients.

Cases	Inflammation of olfactory &respiratory mucosa	Inflammatory infiltration of nerve fibers	Fibrin Deposition & ulcer	Mucosal necrosis	Candida Colonization	Squamous Metaplasia	Sub-epithelial Hyalinization
1	Mild to Moderate	✔	✔ Old Hemorrhage			✔	
2	Mild to Moderate	✔	✔	✔			
3	Mild to Moderate	Not included		✔	✔		
4	Mild to Moderate	Not included	✔		✔		
5	Mild to Moderate	Not included			✔		
6	Mild to Moderate	✔	✔		✔		
7	Severe	Not included	✔		✔	✔	
8	Mild to Moderate	Not included	✔				
9	Severe	Not included	✔				✔
10	Mild to Moderate	Not included	✔		✔		✔
11	Mild to Moderate	Not included					✔

Discussion

Many different mechanisms were presented to explain the high frequency of smell complaints during the course of COVID-19. There are some reports of neuroinvasive characteristics of coronaviruses (1). Therefore, most studies of olfactory dysfunction of COVID-19 focused on the olfactory bulb and related central areas of the brain. However, the ACE 2 receptor, as the main entry molecule for SARA-CoV-2, is

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found frequently in the respiratory epithelial cells of the nasal mucosa. In contrast, olfactory sensory neurons (OSN) of olfactory epithelium do not show this receptor (3). In patients with olfactory disorders following upper respiratory viral infection, Yamagishi et al. showed decreased olfactory receptor cells and nerve bundles (4).

A few studies consider changes in the nasal and olfactory epithelium of COVID-19 patients in English literature. Vaira and colleagues reported respiratory mucosal disruption in one anosmic patient 3 months after the COVID-19 disease (5). Krischenbaum and colleagues showed leukocytic infiltrate in lamina propria, focal atrophy of the mucosa, and inflammatory neuropathy in postmortem sampling of two COVID-19 cases (6). Torabi et al. reported elevated proinflammatory cytokine TNF-α in the olfactory epithelium in patients who died from COVID-19 (7).

In their experimental study, Bryche et al. showed massive olfactory epithelium injury and viral involvement of sustentacular cells, not OSN, with olfactory epithelium‘s inflammatory cell infiltration after nasal instillation of SARS-CoV-2 in golden Syrian hamster (8).

Some imaging studies of the upper nose and olfactory cleft show no or only minor changes (9), meanwhile in a magnetic resonance imaging (MRI) study, Eliezer et al. showed transient obstruction of the olfactory cleft in COVID-19 patients with smell loss (10).

Inflammatory mucosa infiltration was seen in all 11 patients, with ulceration in 9 cases and neuritis in 3 cases. We cannot determine the time of the beginning of these mucosal changes. It can be there during the early days of the disease or after the deterioration of the condition of the patient and ICU admission. Only two patients complained of smell problems in this study, while olfactory mucosal involvement was seen in all cases. Specific objective olfactory tests show a high prevalence of smell problems even in the absence of subjective symptoms (1).

In these severe cases with extensive lung involvement, co-morbidities, and poor constitutional status, anosmia or hyposmia went undiagnosed.

Many factors other than direct viral injury may cause tissue changes in the mucosa, like hypoxia due to lung injury, tissue ischemia or hypo-perfusion because of changes in the cardiovascular system, underlying disease, drugs used for the treatment of disease, high flow oxygen therapy or local manipulation of the mucosa for insertion of nasogastric or nasotracheal tube or effects of BiPAP among others.

Considering the results of this study, we suggest further studies to evaluate the nasal mucosa in healthy non-symptomatic individuals, non-COVID ICU-admitted patients, and outpatient COVID-19 cases. Moreover, advanced histologic studies concurrently with the evaluation of olfaction are beneficial for patients with smell complaint. These studies may clarify the role of the nasal mucosa in the pathophysiology of COVID-19.

Conclusion

We found some pathological findings including inflammatory infiltration in nasal olfactory mucosa in a small group of ICU-admitted patients died from complications of COVID-19. Further studies with larger sample size are necessary.

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Not declared.

Conflicts of Interest

The authors declare no conflicts of interest.

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Ethics

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