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Histological Study of The Effect of COVID 19 on The Olfactory Mucosa of Patients With Post COVID-19 Olfactory Dysfunction

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ABSTRACT

Background: Corona viruses affect both humans and birds. In humans, the symptoms vary from mild cough, sore throat to severe respiratory tract infection and respiratory distress. COVID-19 can be presented by cough, difficult breathing, generalized body aches, loss of smell and taste. The sudden loss of smell was described as a definitive diagnostic symptom of COVID-19 infection. This study was designed to investigate the histological changes of COVID19 on olfactory mucosal epithelium, which was associated with temporary or long lasting olfactory dysfunction.

Patients and Methods: This was a prospective study. Twenty patients with olfactory dysfunction few months after COVID 19 were included and represented the study group. In addition, 20 patients with olfactory dysfunction due to causes other than COVID 19 (e.g., allergic nasal polypi or to skull base fracture) were included as the comparison (control group). All were evaluated in a standard techniques. Then, Forty (40) nasal olfactory epithelium punch biopsies have been obtained under general anesthesia after taking a written consent. Data were recorded and compared between both groups.

Results: The Light Microscopic examination of biopsies in the study group showed inflammatory changes among 17 cases and atrophied changes among 3 cases, compared to 16 and 4 cases in the control group. The inflammatory changes were in the form of inflammatory lymphocytic cells, few macrophages, mast and goblet cells. There was no significant differences between groups regarding patient age, special habits, chronic diseases, complications after biopsy or the result of biopsy. However the duration of OD was significantly longer in the patient than the control group (6 (4-8) vs 2 (1-5) months).

Conclusion: COVID 19 invades nasal olfactory epithelium leading to reversible inflammatory changes that was presented as a reversible olfactory dysfunction. These changes did not differ significantly than other causes nasal inflammation.

Keywords: COVID-19; Olfactory Mucosa; Olfactory Dysfunction.

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INTRODUCTION

Chronic Virus Disease-19 (COVID-19) was firstly discovered in Wuhan in 2019. Caused by Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). It is usually presented with severe respiratory and general manifestations (e.g., cough, fever, tiredness, and difficulty breathing). It is the largest pandemic since the 1918 influenza A virus subtype outbreak. It leads to death of millions of people worldwide. Smell and taste loss was reported as an associations of COVID-19 [1-4].

Different worldwide Organizations (e.g., the American Academy of Otolaryngology) suggested that the sudden-onset loss of smell and/or taste is a diagnostic indicator for COVID-19. This loss of smell was attributed to upper respiratory viral infection, nasal inflammatory changes, nasal edema, and respiratory obstruction [5-7]. However, more recent studies stated that loss of smell or taste should not be used as definitive indicators of COVID-19 infection [8,9].

It seems that, the symptoms of the disease changed over time with appearance of vital mutants. For example, with appearance of Omicron family variants, the incidence of small loss dropped from 50-60% to 12% among Europeans positive for COVID-19, while the estimated global prevalence of anosmia related to Omicron variant is approximately 4% [10].

The post COVID-19 olfactory dysfunction (OD) varies greatly from are to area and from severe to mild diseases. OD is usually transient, disappears after the acute phase of infection (lasts 9-15 days). However, the resolution of OD may be delayed up to 2 years after recovery [11-13].

On the cellular basis, the virus binds to S-protein of the olfactory cells. This leads to cleavage of S-protein and entry of the virus to cell (cell invasion). This was associated with functional disruption of these cells, leading to temporary or permanent OD [14,15].

The self-assessment of olfactory function should not be the only indicator for sure diagnosis of OD. Physical tools must include the use of minimal strength of an odor that can be perceived, discriminated and identified [16].

The use of several chemical showed promising results in treatment of OD after COVID-19. These include intranasal sodium citrate, intranasal vitamin A or systemic omega-3 [17]. We aimed to study the histological effect of COVID-19 on olfactory epithelium in cases with post COVID-19 temporary or long lasting olfactory dysfunction.

PATIENTS AND METHODS

This was a prospective comparative, case control study. This was performed in Al-Zhraa University Hospital (Faculty of Medicine for Girls Al-Azhar University) and Military Medical Complex at Kopri El Koppa, Cairo, Egypt. The primary aim of the study was to determine if COVID19 causes reversible inflammatory changes or irreversible atrophy changes in olfactory epithelium. The study includes 20 patients with olfactory dysfunction few months after COVID 19. In addition, 20 control patients with olfactory dysfunction due to causes other than COVID 19 (e.g., allergic nasal polypi or olfactory dysfunction due to skull base fracture) were included as a comparison (Control) group.

The inclusion criteria were 1) laboratory confirmed COVID-19 (at least 4 weeks after recovery), 2) adult males or females (> 18 years of age) and post-COVID-19 olfactory dysfunction (OD) (for study group) and OD from other causes (for control group).

The Exclusion criteria were 1) Suspected COVID-19 without laboratory confirmation, 2) patients < 18 years old, 3) Patients with COVID-19 with no olfactory dysfunction

Ethical consideration: All study participant (in the study or comparison groups) signed an informed consent to participate and the study protocol was reviewed and approved by the local research and ethics committee from Al-Azhar Faculty of Medicine. The privacy of the patients were assured and data were anonymized by coding. The data was only used for the purpose of the research and all ethical codes of Helsinki declaration were followed up during the study.

Study tools: Firstly, all patients were evaluated on the clinical basis in a standard fashion according to our facility protocol. This was performed by complete history taking (patient characteristics, COVID-19 symptoms & signs and any complications), general and local examination. In addition, a nasal biopsy was performed for histological evaluation of olfactory mucosa. Under general anesthesia, a nasal gauze soaked with adrenaline was introduced. Then, a 4 mm zero degree nasal endoscopy was introduced, a bunch biopsy from the olfactory epithelium in axilla of middle turbinate was obtained by up turned through cutting blakesley. The biopsy was preserved in formalin till the time of examination. Biopsies were prepared and examined by light microscopy after staining by Hematoxylin and eosin

Statistical Analysis: Data were collected, and Fed to the Statistical Package for Social Science (IBM SPSS) version 2023. The parametric quantitative data were expressed as mean, standard deviations, while medians and inter-quartile ranges were used to express in non-parametric data. In addition, qualitative variables were expressed as relative frequencies and percentages. The Chi square test (Fisher exact test when the expected count in any cell found less than 5) was used to study the association between categorical variables, while independent samples "t" (Mann-Whitney test for non-parametric data) test was used to compare two means. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

RESULTS

The Light Microscopic examination of biopsies in the study group showed inflammatory changes (Figure 1) among 17 cases and atrophied changes among 3 cases. The inflammatory changes were in the form of inflammatory lymphocytic cells, few macrophages, mast and goblet cells. In addition, comparable inflammatory changes were reported among 16 control biopsies, while atrophied changes reported among 4 control cases.

Comparing study to control groups, there was no significant differences between groups regarding patient age, special habits, chronic diseases, complications after biopsy or the result of biopsy. However the duration of OD was significantly longer in the patient than the control group (6 (4-8) vs 2 (1-5) months) (Table 1). When we compared cases with atrophied to those with inflammatory changes regardless the cause, we recorded non-significant differences between both groups as regards age, special habit or other chronic diseases (Table 2).

Table (3) showed the post-infectious chronic complications after COVID-19 and there was no significant differences between cases inflammatory than those with atrophied changes. The chest symptoms was reported in 52.9% and 66.7% of the inflammatory and atrophied subgroups respectively. On the other side, chronic fatigue was reported only in 5.9% of the inflammatory group compared to none in the atrophied subgroup.

Table (1): Comparison between control and patients groups regarding demographic data and characteristics of the studied patients

			Control group n = 20	Patients group n = 20	Test value	P-value
Age (year)	Mean ± SD		33.25 ± 10.02	34.6 ± 9.01	0.448	0.657
	Min. – Max		19 – 50	22 – 50		
Special habits	None		9 (45.0%)	11 (55.0%)	0.400	0.527
	Smoker		11 (55.0%)	9 (45.0%)		
Chronic diseases	**Negative**		12 (60.0%)	10 (50.0%)	0.404	0.525
	Positive	Total	8 (40.0%)	10 (50.0%)		
		DM	2 (10.0%)	4 (20.0%)	0.784	0.376
		HTN	5 (25.0%)	3 (15.0%)	0.625	0.429
		Asthma	2 (10.0%)	3 (15.0%)	0.229	0.633
		Chronic Renal disease	1 (5.0%)	1 (5.0%)	0.001	1.00
Duration of OD	Median (IQR)		**2(1-5)**	**6(4-8)**	***5.203***	***<0.001****
Complications after biopsy		No	16 (80.0%)	16 (80.0%)	0.001	1.00
		Epistaxis	4 (20.0%)	4 (20.0%)		
Results of biopsy		Inflammatory cells	16(80.0%)	17(85.0%)	0.173	0.677
		Atrophied	4 (20.0%)	3 (15.0%)		

Table (2): Relation of presence of atrophy with other variables among study population

			Inflammatory cells n = 33	Atrophied n = 7	Test	P-value
Age	Mean ± SD		34.64 ± 9.62	30.57 ± 8.28	1.037	0.306
	Min. – Max.		19 – 50	22 – 42		
Special habits	No special habits		18 (54.5%)	2 (28.6%)	1.558	0.212
	Smoker		15 (45.5%)	5 (71.4%)		
Other chronic Diseases	Free		18 (54.5%)	4 (57.1%)	0.016	0.900
	Positive	Total	15 (45.5%)	3 (42.0%)		
		DM	6 (18.2%)	0 (0.0%)	1.497	0.221
		HTN	7 (21.2%)	1 (14.3%)	0.173	0.677
		Asthma	4 (12.1%)	1 (14.3%)	0.025	0.875
		Chronic renal disease	1 (3.0%)	1 (14.3%)	1.540	0.215

Table (3): Relation of presence of atrophy with presence of other COVID-19 chronic complications among study group

Other complications by Covid19	Inflammatory cells No. = 17	Atrophied No. = 3	Test value	P-value
No	7 (41.2%)	1 (33.3%)	0.303*	0.859
Chest symptoms	9 (52.9%)	2 (66.7%)		
Chronic fatigue	1 (5.9%)	0 (0.0%)		

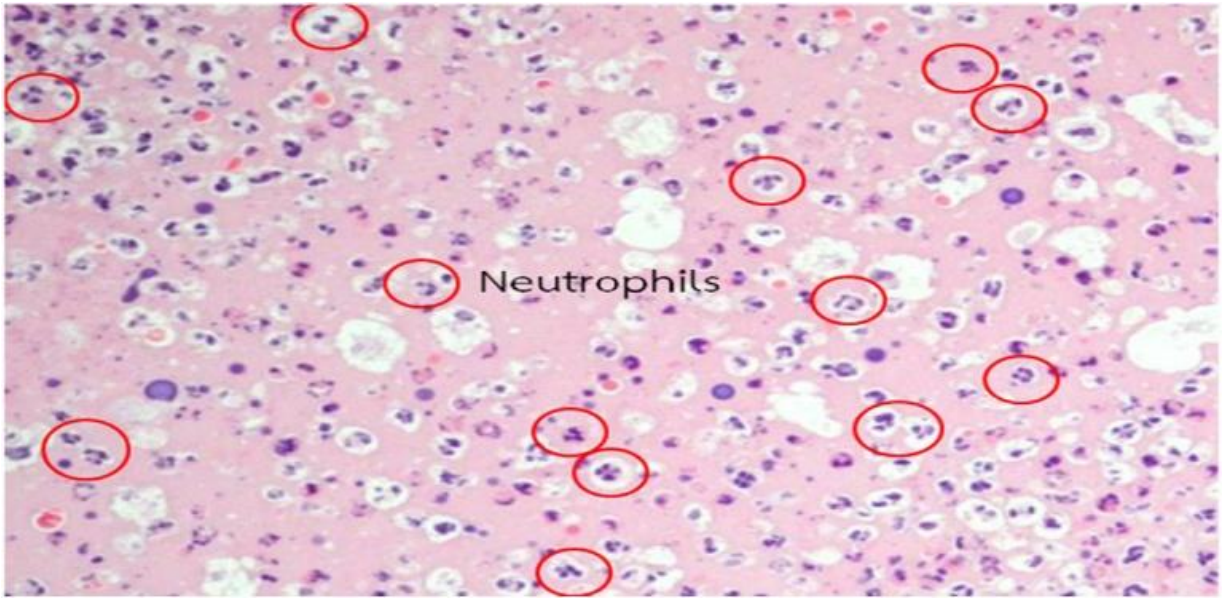

Figure (1): Microscopic examination of the nasal olfactory epithelium of a case with inflammatory changes.

DISCUSSION

This Study aimed to determine the histopathological changes associated with OD after COVID-19 compared to OD after other conditions (chronic rhinosinusitis or post-traumatic). The results revealed that, there was no significant changes between both groups, except significantly longer duration of OD after COVID-19 than after other conditions. These findings confirmed by histopathological examination of the nasal mucosa. These results are in line with **Meng *et al.*** [18] who reported that, the local inflammation of olfactory mucosa is caused by the virus and its invasion via the via the angiotensin-converting enzyme-2 (ACE-2) as the receptor for the SARS-CoV-2. **Wu CT, *et al.*** [19] reported that, specifically, ACE2 is present in the nasal epithelial cells. This explains the inflammatory changes of the nasal mucosa.

Chen S *et al.* [20] reported that, during COVID-19, the SARS-CoV-2 directly binds to nasal epithelia beefing from abundant ACE-2 in the epithelial cells. **Butowt *et al.*** [21] reported that, due to viral invasion, an initial process of inflammation occurred. This is followed by immunological changes which may be responsible for prolonged time of anosmia shown after COVID-19 than other causes (as reported in the current work). **Butowt and von Bartheld** [22] reported that, after initial inflammation, the virus may travel to reach the brain tissue, through contamination of cerebrospinal fluid (CSF). This may explain the permanent or longer duration of anosmia

To explain the changes in olfactory epithelium, it is well-known that, ACE2 is highly expressed in the nasal epithelium, which. The nasal epithelium itself is consisted of two types, the respiratory epithelium (RE) and olfactory epithelium (OE). The RE is thought to have a role in the process of air humidification in the nasal cavity, while OE is utilized for detection of different odors. Odor information is then relayed from the OE to the brain *via* Olfactory sensory neurons (OSN) axons. The OE in turn is composed of sensory neurons, sustentacular (SUS), microvillar, and basal cells [23, 24]. In addition, SUS cells are more likely to be the entry point of SARS-CoV-2 than olfactory neurons and many studies showed that SARS-CoV-2 usually accumulates in SUS cells. SUS cells express high levels of ACE2 and transmembrane protease, serine 2 (TMPRSS2), which are the primary target of SARS-CoV-2 [25-27].

Brann *et al.* [24] proposed that inflammation blocking effective odor conduction, altering the function of OSNs, deteriorating signaling, or causing diffuse architectural damage of the OE may be the mechanisms for OD.

Similar to the histopathology of the current work, it was reported that, the innate immune (inflammatory) cells like neutrophils, monocytes, and macrophages could also produce the desquamation of olfactory epithelium through inflammation [28, 29]. **Bourgon *et al.*** [30] proposed that immune responses make the OE destruction (and OD) worse, suggesting that innate immune cells play a major role in the destruction of OE.

Schwab and Fjaeldstad [31], **Bianco *et al*.** [32] **and Riestra-Ayora *et al.*** [33] reported that, the recovery of the smell after COVID-19 is quite variable in duration (range between 2 to 4 months). However, long olfactory dysfunction is reported an can persist up to 12- 24 months after recovery [34-36]. The results of the

current work reported duration within the reported range.

To summarize, two mechanisms underlying OD occurrence in COVID-19 have been proposed: the infection of SUS cells and the inflammatory reaction of the nasal epithelium. The former triggers OD, the latter likely prolongs OD. These two alternative mechanisms act in parallel; the infection of SUS cells is more important for OD because SUS cells are more likely to be the entry point of SARS-CoV-2 than olfactory neurons. Furthermore, SUS cells abundantly express TMPRSS2 and play a major role in the olfactory epithelium. OD occurrence in COVID-19 has revealed crucial roles of SUS cells. However, the molecular mechanism underlying OD is still largely unknown and the exact mechanisms of OD remain unclear [37], so further research is required.

Conclusion: COVID 19 invades nasal olfactory epithelium that express Angiotensin Converting Enzyme receptors leading to reversible inflammatory changes and reversible olfactory dysfunction, which is not differ greatly than other causes of OD except its longer duration. However, these results must be explained with caution due to small sample size, which is a limiting step of the current work.

Disclosure: None to be disclosed.

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