



Viral cytopathic effect in maxillary sinus epithelium and SARS-CoV-2: Pitfalls in diagnostic characterization

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ABSTRACT

Viral cytopathic effects (VCE) are a well-known phenomenon associated with SARS-CoV-2 infection, especially in the cells associated with the lungs. Because maxillary sinus epithelium expresses angiotensin-converting enzyme 2, cells associated with it are more likely to become infected with SARS-CoV-2 and develop VCE. If VCE is seen in with background of a confirmatory COVID-19 diagnosis, then connecting both become quite convincing. However, the diagnostic problem is expected when a similar VCE is seen without any confirmatory diagnosis of COVID-19. We reported a biopsy sample of maxillary sinusitis in a COVID-19 negative patient. Histopathological examination revealed a pathognomonic VCE in the localized proliferating pseudostratified ciliated epithelium. The only confirmatory aspect linking this VCE with the SARS-CoV-2 was the detection of virus particles at the tissue level. In the present paper, pitfalls and recommendations for future research on this topic are discussed.

1. Introduction

Viral cytopathic effects (VCE) are characteristic features of many viral infections, and SARS-CoV-2 is not an exception to it.^{1,2} Literature has shown VCE in SARS-CoV-2 positive patients at different cellular locations such as type-2 pneumocytes, pneumocytes of unspecified type, and alveolar epithelial cells.^{3,4} The presence of SARS-CoV-2 virus particles within the cytoplasm and nucleus shows various notable features such as nucleomegaly, prominent nucleoli, large eosinophilic cytoplasmic inclusions.⁵ Sertoli cells also show VCE in the form of swelling, vacuolization, and cytoplasmic rarefaction.⁶ In addition, atypical enlarged multinucleated and syncytial pneumocytes are commonly seen in COVID-19 lungs.⁵ The maxillary sinus lining also expresses the ACE2 receptor,^{7,8} hence the VCE is also expected in the lining epithelium. However, to date, no such report has been published in the literature. If these features are seen with the background information of confirmatory diagnosis of COVID-19, then connecting it with VCE becomes quite conceivable. However, the diagnostic problem is expected when a similar VCE is seen without any confirmatory diagnosis of COVID-19.

On similar lines, we report a VCE in the maxillary sinus epithelium and propose its attribution to the SARS-CoV-2. The diagnostic pitfall in the characterization of VCE as attributed to SARS-CoV-2 has been

discussed along with the need for detection of virus particles at tissue level using immunohistochemistry.

2. Case report and discussion

A 26-year-old female reported pain, pressure, and stuffiness in the maxillary sinus for one year. The patient gave a history of intermittent exacerbations and remissions of the condition. There was no previous history of COVID-19 infection and recently done RT-PCR also showed negative results. Based on the clinical and imaging findings, a diagnosis of maxillary sinus infection was made and the affected lining was surgically removed using an intra-oral approach.

The maxillary sinus lining was found to be composed of pseudostratified ciliated columnar epithelium with an intact basement membrane. The underlying stroma showed mild to moderate chronic inflammatory cell infiltration, which was composed mainly of lymphocytes and plasma cells. In a few places, necrotic areas were evident. There was no evidence of eosinophils, thus ruling out the allergic sinus pathology.

At two locations, a very distinctive and unusual proliferation of the sinus epithelium lining in the form of an isolated mass of cells was seen (Fig. 1A). The cells in the mass showed very peculiar VCE in the nucleus

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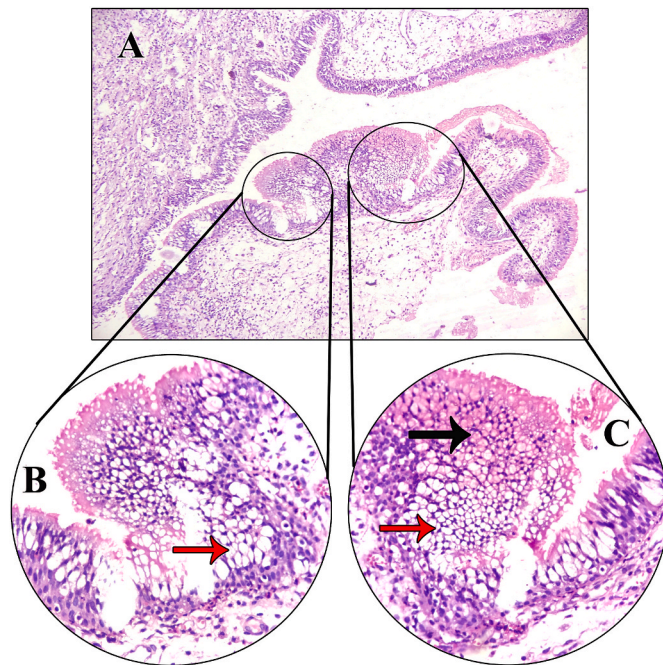


Fig. 1. A photomicrograph of the maxillary sinus lining shows pseudostratified squamous epithelium with focal proliferation (black circle) and chronic inflammatory cell infiltration, indicating maxillary sinusitis (1A). High power magnification of proliferated epithelium shows enlarged swollen cells with clear cytoplasm with shifting of nucleus to one side (red arrow) and cells with eosinophilic cytoplasm resembling inclusion bodies (black arrow).

as well as cytoplasm. The cells were swollen and showed two groups of cells. One group of cells was composed of eosinophilic cytoplasm (suggestive of inclusion bodies) (Fig. 1 B and C, black arrow), while the second showed clear cytoplasm (Fig. 1C, red arrow). The nucleus was pyknotic and shifted to one side of the cytoplasm due to the pushing effect of cytoplasmic content. These features were quite similar to the VCE seen at pulmonary epithelium in COVID-19 patients.^{3–6} Since the patient did not give a history of COVID-19 infection in the past and her recent RT-PCR report was negative, we speculated that the patient might have had an undiagnosed asymptomatic infection of COVID-19 in the past. The rapid antigen test could have ruled this out, but the patient has been fully vaccinated with the AZD1222 (ChAdOx1) vaccine.

Under such a dilemmatic situation, the only confirmatory diagnostic modality to prove that VCE is associated with SARS-CoV-2 could be immunohistochemistry or in situ hybridization on the tissue sample with the main focus on the localized proliferation of sinus epithelium. In this regard, previous studies have shown viral proteins using the IHC technique in alveolar pneumocytes, alveolar macrophages, hyaline membranes, tracheobronchial respiratory epithelium, and minimally in endothelial cells.⁹ However, due to lack of resources, we were not able to perform IHC and hence, the VCE seen in the present case cannot be linked with the SARS-CoV-2 infection.

During the 2002–2003 SARS outbreak, the immunohistochemistry technique for detecting SARS-CoV-2 in formalin-fixed tissue samples was developed.¹⁰ During the COVID-19 pandemic, Liu et al. developed similar assays for SARS-CoV-2 by evaluating commercially available antibodies with SARS-CoV-2 epitopes and SARS-CoV-2 specific glycoproteins.¹¹ To further expand the repertoire of commercially available antibodies and show their utility on autopsy and surgical specimens, Rocha et al.¹² investigated specimens of lungs, placenta, and kidney.

They provided a detailed protocol for different commercially available antibodies for readily implementation in pathological laboratories.¹²

3. Conclusion

This is the first case report that envisages the presence of VCE in the maxillary sinus lining. Some COVID-19 symptoms, such as nasal congestion, sinus fullness, loss of smell sensation, nasal discharge, running nose, sneezing (Omicron variant), and so on, are similar to common nonspecific sinusitis. Surgical removal of the affected lining is a routine part of day-to-day practice. As RT-PCR might be negative, it becomes of paramount importance to check the resected surgical specimen for any evidence of the SARS-CoV-2 virus. Hence, it is recommended for every such specimen to undergo immunohistochemical testing for SARS-CoV-2 virus particles. A provision at every pathological practice should be made mandatory, as this will contribute to a better understanding of COVID-19 pathogenesis. We also recommend a retrospective study on maxillary sinusitis specimens collected during the COVID-19 period for the possible presence of VCE. Perhaps in the future, this might become a marker of identification and detection of undiagnosed cases of COVID-19.

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Declaration of competing interest

All the authors associated with the present manuscript declared no potential conflict of interest concerning the research, authorship, and/or publication of this article.

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