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Impact of COVID-19 on Ophthalmic Pathology

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Abstract

The Coronavirus disease-19 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) remains a significant concern to the public and a major challenge to healthcare workers. Although vaccination programs are generally regarded as successful, recent reports have shown that vaccine effectiveness is decreasing gradually, particularly as booster uptakes are low. The next pandemic is unpredictable and inevitable. Therefore, understanding the impact of COVID-19 on different aspects of healthcare will aid in adaptation to life with pandemics and enable prioritization of medical treatment. The SARS-CoV-2 outbreak significantly changed all sectors of healthcare. Ocular oncology and pathology practices were adapted to adjust to the many new challenges the COVID-19 pandemic presented. This review highlights laboratory modifications and shows how the number, type, and histology of eye oncology cases were impacted during the pandemic.

Keywords: COVID-19; Laboratory; Ophthalmology; Pathology; Ocular; Orbital; Tumor

Abbreviations: COVID-19: Coronavirus Disease-19; GKRS: Gamma Knife Radiosurgery; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; WHO: World Health Organization

Introduction

SARS-CoV-2 was first reported in China on December 2019. By January 2020, the World Health Organization (WHO) announced the COVID-19 outbreak as a public health emergency of international concern [1,2]. As of March 10, 2023, more than 676,000,000 cases of COVID-19 have been reported worldwide [3,4]. The number of reported COVID-19 cases has declined over time. This may be due to a high number of unreported cases following home testing or because individuals are less likely to seek treatment for mild symptoms, particularly in cases of vaccination or prior infection [5]. However, there have been several fluctuations in the number of COVID-19 cases throughout the pandemic years, and it is clear that even with widespread vaccination, COVID-19 will not be completely eradicated [6]. Moreover, the probability of the emergence of new pandemics with similar impacts is approximately 2% each year [7]. The COVID-19 pandemic led to extensive changes to the healthcare system and the suspension of several medical and surgical services including histopathology and ocular oncology services. The consequences of the disruption were most severe on children, older adults, and immuno-compromised patients such as those with malignancies [5]. Patients with cancer are more vulnerable to infection and COVID-19-related systemic complications due to their weak immunity secondary to cancer, anticancer therapy, and overall health status. Studies have shown that cancer patients have a two-fold higher risk of COVID-19 infection than the general population with an approximate 20% increase in mortality rate [8,9]. The effect is not confined to the higher risk of COVID-19 infection but

also includes delays to diagnosis and management of existing conditions. Interruptions to ophthalmic oncology and pathology services may lead to disease progression, increase in tumor size, loss of vision, metastasis, and poor survival, especially in aggressive malignancies such as retinoblastoma, melanoma, and sarcoma [5]. Applying the guidelines and appropriate precautions is required, as well as maintaining a balance between providing appropriate treatment and care and reducing the risk of COVID-19 infection [10].

COVID-19 Histopathology Laboratory Instructions

The impact of COVID-19 on oncology services is not limited to the patient, but all of the oncology team and health personnel who are involved in the management approach. Biopsy or excision of the tumor incorporates risk to the pathologists and technicians who deal with specimen storage, transportation, and examination. Therefore, adequate precautions and safety measures should be applied throughout the procedure. Histopathology services are divided into three phases: pre-analytic, analytic, and post-analytic.

The Pre-Analytic Phase: The pre-analytic phase includes receiving fresh or formalin-fixed tissue, gross examination, cutting, and slide processing [11]. This phase is of the greatest concern due to the risk of infection transmission during tissue handling. Division of the specimen into surgical pathology, microbiology, flow cytometry, and molecular genetics should be carried out in the operating room, followed by direct submission to the intended laboratory. This will decrease the handling risk of transferring the whole sample to the surgical pathology department for division [12]. The samples should be labeled correctly as COVID-19 biohazard and stored in double containers with a secure lid to minimize the spill. The tissue should be kept in an adequate amount of formalin (1:10 ratio) and glutaraldehyde for 24-48 hours to ensure proper fixation and decrease infectivity. During specimen examination and grossing, pathologists must wear gloves, disposable gowns, and medical masks with shields or goggles. Disinfection reagent should be applied to the external surface of the containers prior to opening, and work surfaces should be decontaminated after specimen examination. A frozen section is sometimes required in some eye lesions in order to confirm the diagnosis and assess the surgical margins. As a general rule, frozen sections for pathology samples of confirmed or suspected COVID-19 patients should be deferred if possible due to the potential for aerosol production and to avoid infection risk. Communication between the pathologist and the clinician is essential to assess the value of the frozen section in the management of the case and to prepare the laboratory in advance. If unavoidable and necessary for the patient's outcome, the frozen section should be performed in a small confined area, taking all the proscribed protection precautions, followed by discarding the staining solution and decontamination of the cryostat [13-16].

The Analytical Phase: The analytical phase relates to slide interpretation under the microscope and surgical pathology report preparation [11]. This step involves handling of the slides by different personnel, who are required to wear gloves or immerse the slides in 95% alcohol before they reach the pathologist. Pathologists should also wear gloves, wash their hands frequently, or use alcohol hand sanitizers, and should, in addition, decontaminate the workspace, including the microscope, keyboard, and phones [17]. Work schedules have been changed to ensure physical distancing and to reduce infectivity during slide analysis. The use of digital pathology/telepathology increased after many institutes introduced remote working or working from home. This is an easy way to examine the tissue microscopically in high resolution and without face-to-face contact or on-site presence in the lab. Additionally, digital pathology facilitates image sharing between pathologists to obtain a second opinion quickly and easily [5]. The engagement of digital and online applications in routine work schedules is an example of a positive change as a result of the COVID-19 pandemic.

The Post-Analytical Phase: The post-analytical phase is the final phase and includes tissue disposal [11]. Care should be taken to insure safe and proper residual tissue disposal, which should be discarded in properly sealed double-layered and leak-proof waste bags or containers. The outer surfaces should be disinfected and an infection biohazard label attached. If the specimen is COVID-positive or COVID-suspected, it should be clearly labeled as a COVID-19 specimen and discarded separately following institutional protocol [13-16].

Impact of COVID-19 on the Number of Ophthalmic Histopathology Samples

The sudden appearance and rapid spread of the COVID-19 pandemic resulted in the shift of most healthcare's toward COVID-19-related services. Additionally, the reduction in manpower, due to illness, quarantine, or after implementation of physical distance rules, resulted in a reduction in work volume. There was a decline in the number of surgical procedures, particularly in the case of elective and non-urgent surgeries. Consequently, the number of received samples and histo-pathological diagnoses declined [18,19]. A Dutch study compared the numbers of pathology specimens in 2019 and 2020. The sample number decreased by more than 85% during the first COVID-19 lockdown period (March 16-June 1, 2020). The decrease was observed

in all sample types; however, malignant cases were the least affected [18]. A similar study in India assessed the effect of the COVID-19 pandemic on the presentation of ocular and periocular tumors. The cross-sectional study included 5,811 patients between March 25, 2017 and March 31, 2021. They found an 85% decrease in the number of cases during the lockdown phase (between March 25, 2021 and May 31, 2021) and similarly, malignant cases were less affected than benign cases [20].

In Brazil, a retrospective study evaluated the impact of the COVID-19 pandemic on the number of new cases and therapeutic approaches in ocular oncology. The number of new cases in the pre-pandemic period (from March 2019 to September 2019) was 122, while in the pandemic period (from March 2020 to September 2020), the number of new cases was 64. This represents an approximate 48% decrease in the new cases referred to the ocular oncology service, and, as in the previous studies, a higher proportion of malignant cases were seen in the pandemic period compared to benign cases [21]. These results demonstrate the decrease in the overall number of ocular pathology specimens, particularly during the first COVID-19 wave, with a higher proportion of malignant samples taken compared to benign samples. Over time, the number of surgeries increased gradually as a result of the increase in public awareness, hospital organization and timely preventive measures.

Impact of COVID-19 on Specific Eye Pathology

Eyelid Skin Tumors: Most ocular skin tumors are related to the eyelid. Malignant eyelid tumors include basal cell carcinoma, squamous cell carcinoma, melanoma, sebaceous cell carcinoma, and Merkel cell carcinoma. The standard management for eyelid malignancy is surgical excision followed by reconstruction. During the COVID-19 pandemic, the treatment approach for malignant eyelid tumors did not change, however, benign tumors and non-suspicious lesions could be observed or surgically postponed. In all situations, physicians should comprehensively explain the risks and benefits to their patients [5]. All skin excisions should be sent to the surgical pathology laboratory for diagnosis and to ensure a clear microscopic margin. Usually, skin biopsies constitute the majority of general surgical pathology specimens. The largest proportion of skin biopsies is for benign lesions [18,22]. However, van Velthuysen, et al. observed a decrease of approximately 70% in all skin cases during the COVID-19 first lockdown period. One possible reason for this is that skin disease may not cause severe pain or life-threatening symptoms, which may have led to delays in patients presenting to hospitals during the pandemic crises [18]. Accordingly, most skin surgeries were performed on cases of rapidly growing lesions or where malignancy was suspected.

To assess the effect of diagnostic delay as a result of COVID-19 on skin malignancies, a Dutch study compared the pathology reports for melanoma and squamous cell carcinoma cases registered between 2018 and 2021. In a total of 20,434 primary skin melanoma, a slight increase in pT stages was found during the first lockdown period (March 12, 2020 to May 31, 2020), and no significant differences in the mean Breslow thickness were observed between the pre-COVID-19 and COVID-19 periods. For squamous cell carcinoma, 68,832 cases were included in the study, and no significant change in pT stages was found. The results from this study, and other similar studies [23-25] indicate that the COVID-19-diagnostic delay in skin melanoma and squamous cell carcinoma had little impact on tumor characterization. However, a separate Dutch study evaluated the effect of COVID-19 on advanced melanoma cases (stage IIIc and IV melanoma) and found severe delay to systemic therapy and a significant increase in the number of patients who presented with brain metastases [26]. Thus, clinico-pathological features including the stage and grade of malignant tumors at presentation should be taken into account as important factors in predicting the effect of treatment delay.

Conjunctival Tumors: Conjunctiva is a COVID-19 point of entry and source of infection. COVID-19 RNA has been detected in the conjunctiva and tears of patients with COVID-19. Furthermore, in some cases, conjunctivitis is the only presenting sign of COVID-19 infection. One of the first physicians to recognize the novel SARS-COV-2 virus in 2019 was the ophthalmologist Dr Li Wenliang who died in 2020 after contracting COVID-19 from an asymptomatic patient [27-29]. As exposure to the ocular surface may transmit the infection all preventive measures, including eye protection with goggles and face shields, are essential [8,29,30]. Malignant ocular surface tumors include squamous cell carcinoma (the extreme of a spectrum ocular surface squamous neoplasia), melanoma, and lymphoma [31]. The gold standard in the management of malignant conjunctival lesions is long established to be surgical excision, which is preferred to minimize hospital visits. Topical chemotherapy is an alternative treatment modality, particularly in COVID-19-positive patients, to prevent surgical exposure [5]. Both approaches should be considered, and the choice between surgical vs. topical treatment depends on the patient's overall condition and surgical margin status [32,33]. Conjunctival squamous cell carcinoma was the most common diagnosis in ocular oncology services during the COVID-19 pandemic. The treatment approach was modified during the period in favor of non-invasive treatment and fewer surgeries to reduce hospitalization and risk of infection. There was an increase in the use of topical therapy (+10%) and reductions

in the number of performed surgeries (-7%) and follow-up visits [21]. It should be noted that surgical treatment for benign ocular tumors can often be delayed [5].

Orbital Tumors: Malignant orbital tumors can affect vision, cause permanent disability, or even death, particularly if malignant or fast-growing. Common malignant orbital tumors include rhabdomyosarcoma, lacrimal gland carcinoma, lymphoma, and orbital metastasis. These malignancies require instant recognition and a proper management approach without delay. Diagnosis of orbital tumors requires orbitotomy with incisional/excisional biopsy. In advanced cases, orbital exenteration might be needed. Protection in accordance with the guidelines should be applied throughout the management process and pathologists should be informed in advance if frozen section is required [5]. Complications associated with COVID-19 infection and vaccination has been reported. COVID-19 infection can be associated with an increased risk of secondary infections, such as mucormycosis. Multiple cases of rhino-orbital-mucormycosis have been diagnosed during active COVID-19 or the recovery period, particularly in patients with uncontrolled diabetes mellitus. This indicates that the risk of orbital mucormycosis may be increased during and after COVID-19 infection due to long-term immune disturbance in COVID-19 patients. Therefore, it is important to be aware of this lethal orbital complication and the need for careful monitoring of patients at risk [34-37]. In addition, a case of orbital pseudotumor was identified in a 40-year-old healthy woman one week after she received the first dose of the COVID-19 vaccine. The systemic workup including infection and autoimmune investigations was normal. This case might also represent an immunological response against orbital tissue [38]. Although the exact cause or relation to COVID-19 vaccination is not confirmed, the immunological effect of the COVID-19 virus and/or vaccine should be taken into consideration.

Retinoblastoma: Retinoblastoma is the most common primary malignant intraocular tumor in children. It is considered a high priority in which early detection is essential to preserve the patient's life and vision [39]. Management of retinoblastoma including systemic intravenous chemotherapy, interventional intra-arterial chemotherapy, or enucleation, cannot be delayed or changed. Bone marrow biopsy and/or cerebrospinal fluid cytology might be required as part of systemic screening. Additionally, genetic testing is required to evaluate and determine the risk in family members [5]. This broad and multidisciplinary approach necessitates careful adherence to safety precautions to reduce the infection risk for patients and health personnel. A cross-sectional study in India assessed the effect of COVID-19 lockdown on retinoblastoma patients. The study included 326 patients undergoing management during the lockdown period from March 2020 to the end of June 2020. More than 35% of patients were lost to follow-up, while 60% returned after delays ranging from 8-80 weeks. The delays resulted in treatment interruption and subsequently worse outcomes including intracranial extension and death [40]. The availability of therapeutic interventions provided by hospitals was also affected. A multi-center, multi-national survey by Fabian, et al. revealed a decrease in treatment modalities during the pandemic, including examinations under anesthesia, enucleation, and chemotherapy [41]. This further complicated the situation and adversely affected management plans.

Uveal Melanoma: Uveal melanoma is the most common primary malignant intraocular tumor in adults. The prognosis depends on several clinico-pathological features such as tumor size, location, histological cell type, and underlying genetics [39]. Due to its aggressive nature, the element of time is important in the diagnosis and treatment process. Tumor sampling is helpful to acquire accurate histological and genetic features to confirm the diagnosis and assess risk of metastasis. Management options include eye-saving brachytherapy and enucleation [5,39]. In a normal situation, plaque radiotherapy is the first choice to preserve the eye globe while enucleation is indicated for advanced cases such as large-size tumors with secondary glaucoma or retinal detachment [42]. Parker, et al. suggests that gamma knife radiosurgery (GKRS) is an effective treatment method for uveal melanoma with a reliable rate of tumor control. In addition, the limited hospital visit time means that it can be considered a good treatment option during the pandemic [43,44]. An Irish study compared the clinico-pathological features and treatment modalities for uveal melanoma cases from January 2019 to December 2020. The results show that patients who presented in 2020 had more advanced diseases with increased basal diameter, thickness, and extra-scleral extension compared to those in 2019. From a treatment standpoint, more patients underwent enucleation than radiotherapy (21% vs. 9% respectively), and the duration for radiotherapy was longer than that in 2019 [45]. Ocular pathologists and oncologists should also consider the possibilities of COVID-19 vaccine changes on uveal melanoma. A recent report of a patient with necrotic uveal melanoma following receipt of the second dose of the COVID-19 vaccine is suggestive of vascular thrombosis induced by the vaccine. Histologically, the largest proportion of the tumor was necrotic with tumor ghost cells and melanophages, while the viable melanoma cells were confined to the periphery of the tumor. Although unconfirmed, the association of COVID-19 with thrombotic events has been reported [46-48]. This indicates the wide-ranging impacts of COVID-19 on the histopathology of tumors for which it is vital that medical professionals are aware of, particularly in light of the

distribution of vaccination globally.

Conclusion

The fluctuation in infection rates and the emergence of new variants makes it clear that COVID-19 remains an ongoing threat to public health and that it will not be the last pandemic. In response to COVID-19, several changes to working practices have been introduced by ocular oncology and histopathology departments. This article summarizes these adaptation strategies and describes the histopathological changes associated with COVID-19. Constant updates of such reports are important to provide an optimal, yet safe, management approach.

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