Bilateral Conjunctivitis, Keratitis, and Anterior Uveitis in a Patient Co-infected with Parvovirus B19 and SARS-CoV-2

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Abstract
Parvovirus B-19 (B19V) is a common infection in children, occasionally complicated by ocular manifestations. In patients infected with severe acute respiratory syndrome virus (SARS-CoV-2), many cases of bacterial, fungal, and viral co-infections have been described. We report on a case of bilateral conjunctivitis, keratitis, and anterior uveitis that occurred in a patient co-infected by B19V and SARS-CoV-2. A young nurse developed, 20 days after the onset of asthenia and fever, a maculopapular rash and, in the following month, B19V-related arthritis. Shortly after a course of antibiotics and corticosteroids and the resolution of the arthritis, she began to complain of hearing loss and tinnitus. A polymerase chain reaction for SARS-CoV-2, previously negative, turned out positive; IgM for B19V decreased while IgG increased and antinuclear autoantibody and rheumatoid factor test results were positive. Ear symptoms disappeared after a course of prednisone, but eye burning and itching appeared 2 weeks after the coronavirus disease 2019 (COVID-19) positive swab. Bilateral conjunctivitis, keratitis, and anterior uveitis were diagnosed, which responded completely to a topical corticosteroid and mydriatic therapy. No relapses were observed in the following 12 months. The onset and progression of the symptoms, along with the laboratory findings, suggest a double pathogenesis of the ocular manifestations: keratitis and uveitis, along with the ear symptoms, seem to be the expression of an autoimmune reaction to B19V infection, while the conjunctivitis was likely related to direct infection of the conjunctiva by SARS-CoV-2.
Introduction

Infection with parvovirus B19 (B19V), a small single-stranded DNA virus of the family Parvoviridae [1–3], is very common and occurs seasonally in temperate climates worldwide, particularly in winter and spring [2, 4]. The spectrum of the clinical manifestations associated with B19V infection depends on the age and immunologic and hematologic status of the host [2–5]. In children, B19V is the cause of erythema infectiosum, also referred to as the fifth disease. Its characteristic symptoms are fever, an initial “slapped cheek” facial rash that later spreads to the trunk and limbs as a maculopapular rash, arthralgia, and arthritis [1–5]. In adults, particularly in women, arthropathy is more common, mostly in the form of symmetric polyarthritis or polyarthritis with a rheumatoid-like distribution [2–6]. Parvovirus infection rarely involves the ears and eyes, and these manifestations, apart from conjunctivitis, which appears during the acute phase, are probably delayed symptoms due to autoantibody formation, such as antinuclear antibodies (ANAs) and rheumatoid factor (RF) [3, 5, 7–10].

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome virus (SARS-CoV-2), is a global healthcare crisis [11]. The main symptoms concern the respiratory tract [12, 13], but it can also affect the cardiovascular, neurological, and gastrointestinal systems, as well as the eyes [12–14]. Since the beginning of the COVID-19 pandemic, several cases of co-infection with one or more other pathogens have been reported; the most common secondary infections are bacterial and fungal, but cases of viral co-infection have also been described, particularly influenza A [15–17]. We report on a case of conjunctivitis, keratitis, bilateral anterior uveitis, hearing loss, and arthritis in a young adult female infected by parvovirus B-19 and, subsequently, by SARS-CoV-2.

Case Presentation

A 39-year-old nurse complained of asthenia and fever on 27 December 2020. Given the COVID-19 pandemic and the occupational risk factor, she decided to perform a rapid antigen test for SARS-CoV-2, with a negative result. The symptoms persisted until 17 January 2021, when a maculopapular rash on the trunk and limbs appeared. A polymerase chain reaction for SARS-CoV-2 was again performed with a negative result. On 10 February 2021, the patient complained of bilateral arthralgia in her elbows, knees, and wrists. She was admitted to the emergency room of our hospital and tested positive for parvovirus B-19 infection (IgM 30.5 U.A.; IgG 7 U.A.). She was diagnosed with infectious arthritis, and prednisone (25 mg/day), amoxicillin (875 mg), and clavulanic acid (125 mg, twice daily) were administered. Symptoms disappeared in 7 days, and the therapy was completely stopped after 14 days. On 2 March 2021, the patient began to complain of bilateral hearing loss and tinnitus. A polymerase chain reaction for SARS-CoV-2 showed a positive result, although the patient did not complain of any typical symptoms of SARS-CoV-2 infection. An audiological examination and audiogram showed bilateral sensorineural hearing loss. At that time, IgM for parvovirus had decreased (11 U.A.) and IgG had increased (20.5 U.A.), while ANA (1:80 dotted pattern) and RF (60 UI/mL) tests were positive. The patient started oral therapy with prednisone (25 mg/day) for a week with a subsequent quick withdrawal. She showed improvement and then a complete resolution of ear symptoms, while on 13 March 2021 eye symptoms (burning and itching) appeared. Within 3 weeks, a SARS-CoV-2 swab showed a negative result, and during this time, no systemic COVID-19-related symptoms were present. On 17 March 2021, the woman, having completed the above therapies, began to complain of discomfort and photophobia in both eyes. At our first observation, on 22 March 2021, we...
found in both eyes a best-corrected visual acuity of 20/20; conjunctival hyperaemia with tarsal follicles; mild ciliary injection; diffuse subepithelial discrete keratic infiltrates; small, fine endothelial keratic precipitates; 1+ flare and cells in the anterior chamber; and no posterior synechiae. No relative afferent pupillary defect was observed. Vitreous and fundus examinations were within normal limits. The intraocular pressure was 12 mm Hg in the right eye and 13 mm Hg in the left. Optical coherence tomography (OCT), Optical coherence tomography angiography, and fluorescein and indocyanine green angiography were normal. The patient was given dexamethasone q.i.d. and tropicamide b.i.d. eye drops, and both the corneal and uveal inflammation subsided in 1 week. The therapy was slowly reduced and stopped in 4 weeks without any conjunctivitis, keratitis, or uveitis relapses during the following 12 months of follow-up.

Discussion and Conclusions

Uveitis associated with B19V infection is more frequent in childhood. Ito et al. [9] described a case of bilateral panuveitis in a 9-year-old boy who developed redness of the conjunctiva, severe iritis (3+ cells), bilateral papilloedema, and dye leakage from retinal vessels detected by fluorescein angiography. Maini et al. [10] reported a case of a 6-year-old girl with unilateral non-granulomatous anterior uveitis (3+ anterior chamber cells) who, 2 months after the anterior uveitis, developed mild disc oedema with hypotony (4 mm Hg) and then a contralateral panuveitis. Finally, Corridan et al. [18] described an 18-year-old girl with bilateral anterior uveitis with ciliary injection, large keratic precipitates occurring predominantly in the corneal periphery, tonic pupils, mild anterior vitritis, and left optic disc hyperaemia. Only 1 case of bilateral anterior uveitis with acute parvovirus infection in a young woman has been reported so far [19]. Conjunctivitis is another possible ocular manifestation of B19V infection, which has been described concomitantly with the cutaneous lesions, thus suggesting a direct role of the virus in its pathogenesis [20–22]. Punctate corneal epitheliopathy and corneal anaesthesia due to the damage of ciliary ganglion has been reported in another subject [18].

In our patient, we observed simultaneous conjunctivitis, keratitis, and anterior uveitis during B19V and SARS-CoV-2 infections. To the best of our knowledge, these findings have never been reported before. Conjunctivitis has only been described in the early period of B19V infection [20–22], while in our patient it appeared 3 months after the diagnosis of parvovirus disease. On the other hand, in COVID-19 disease, conjunctivitis is quite typical (0.8–31.6% of cases) [23–25] and, in some cases, it might be the only manifestation of COVID-19 [25]. Therefore, in our case, conjunctivitis seems to be much more related to a SARS-CoV-2 direct infection than to B19V, while the presence of another viral infection of the conjunctiva concomitantly present with SARS-CoV-2 is very unlikely in an immunocompetent patient.

The pathogenesis of uveitis associated with parvovirus B19 is still unclear. Some authors support the hypothesis that a direct invasion of the virus is responsible for the ocular manifestations [9], while others suggest a possible autoimmune reaction [10]. Indeed, ANAs were detected in 65% of patients with a B19 infection [26] and the autoantibodies seem to play an important role in the development of uveitis. In our patient, eye and auditory lesions appeared when the patient’s blood tests showed a progressive reduction of B19V IgM, a gradual increase of B19V IgG and positive testing of RF and ANAs. All these results state the possibility of an immune-mediated reaction of both the auditory and ocular systems, which might have been fostered by insufficient and short-term steroid therapy during acute B19V infection. The SARS-CoV-2 infection, which appeared concomitantly with the
auditory symptoms and prior to the ocular diseases, seems to be more related to the occupational risk of our patient than to an immunodeficient condition leading to a double viral infection.

Interestingly, we did not detect any posterior segment involvement of the eye, either clinically or instrumentally. The absence of inflammation in the posterior segment of the eye seems more typical of ocular B19V infection in adults than in children. Therefore, it can probably be assumed that papillitis is a more typical manifestation of B19V infection during childhood. Conversely, the most frequent ocular manifestations in COVID-19 are represented by retinal involvement [27–29] and, therefore, the absence of posterior segment lesions does not support the role of SARS-CoV-2 in the pathogenesis of the uveitis in our patient.

In conclusion, if we consider the time elapsed between both the B19V and the SARS-CoV-2 infections and the onset of the ocular manifestation; the changes over time of IgM and IgG antibodies against B19V; the appearance of RF and ANAs; and the period elapsed between the positive SARS-CoV-2 test and the onset of conjunctivitis, we can suppose that our patient has presented a double pathogenesis of the ocular diseases. The conjunctivitis was probably more related to a direct SARS-CoV-2 infection of the conjunctiva, while the keratitis and uveitis seem to be expressions of an autoimmune reaction driven by the B19V infection. Nevertheless, a short course of topical corticosteroids was able to quickly resolve all of the ocular manifestations.

**Statement of Ethics**

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

**Conflict of Interest Statement**

All the authors report no conflict of interest.

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**Author Contributions**

Maria Carmela Saturno: substantial contributions to the conception and design of the study; acquisition, analysis, and interpretation of data; drafting the manuscript and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Priscilla Manni: contributions to the conception and design of the study; acquisition, analysis, and interpretation of data; and revision and approval of the final version. Massimo Accorinti: contributions to the conception and design of the study; acquisition, analysis, and interpretation of data; and revision and approval of the final version.
Data Availability Statement

All the data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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