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D.K. Kamalova[1,3*], M.G. Makibayeva[2], A.O. Amirgazin[1], S.T. Abdrakhmanova[2], I.I. Sytnik[1], A.A. Tuleubaeva[2], E.M. Ramankulov[1], A.B. Shevtsov [1]

[1]National Biotechnology Center, Astana, Kazakhstan
[2]Astana Medical University, Astana, Kazakhstan
[3]L.N. Gumilyov Eurasian National University, Astana, Kazakhstan
*e-mail: kamalova@biocenter.kz

CURRENT ASPECTS OF THE CLINICAL COURSE OF COVID-19 IN CHILDREN. CLINICAL CASES

Abstract. In the pediatric population, coronavirus infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is more commonly observed in asymptomatic and moderately symptomatic cases. However, when COVID-19 coexists with other infections, it can result in a more severe disease progression. Various subtypes of the SARS-CoV-2 virus are associated with different clinical presentations, with certain subtypes exhibiting a predominance of specific symptoms or manifestations. Clinical manifestations of COVID-19 in children, both during the acute phase of the disease and in the post-COVID-19 period, are not fully understood and different compared to adults. This article presents four clinical cases in which PCR-confirmed COVID-19 was observed in combination with infections caused by viruses such as Ebstein-Barr, varicella, and rotavirus. The severity of the disease in these cases was attributed to symptoms related to intoxication, as well as skin and intestinal syndromes. To understand important genomic signatures of SARS-CoV-2 virus circulating in the area, the genome-wide sequencing was performed for the SARS-CoV-2 samples isolated from nasopharyngeal swabs collected from four patients.

Based on the genotyping results, all four samples were found belonging to the SARS-CoV-2 virus Omicron lineage. Three months after the initial testing, follow-up evaluations of the children indicated a higher likelihood of complete recovery. However, some underlying disease manifestations, including anemia and atopic dermatitis, persisted despite the resolution of COVID-19 symptoms.

Key words: COVID-19, SARS-CoV-2, PCR, children, dermatological manifestations, post-coV syndrome, sequencing.

Introduction

The COVID-19 pandemic originated in 2019 in China, has affected a vast number of individuals, with over 676 million people diagnosed positive and sadly resulting in more than 6.8 million deaths (source: https://coronavirus.jhu.edu/map.html). Early epidemiological studies have indicated that the primary symptoms of the disease typically include fever, dry cough, shortness of breath, and headache. In some cases, the disease can progress to pneumonia, further complicating the condition. [1, 2]. As the disease continues to spread and the number of cases rises globally, there have been reports of non-specific presentations of COVID-19. Patients with a severe form of the disease are at a higher risk of experiencing neurological dysfunction, such as impaired consciousness, as well as skeletal muscle damage. These manifestations demonstrate the wide-ranging impact of COVID-19 on various organ systems beyond the respiratory system. [3]. Numerous studies have provided evidence of active replication of the SARS-CoV-2 virus in the gastrointestinal tract. This has been observed in clinical cases where patients present with intestinal infections, sometimes involving the liver, of varying severity. These findings highlight the potential involvement of the gastrointestinal system in COVID-19 and the need for further research to understand the mechanisms and implications of this aspect of the disease [4]. COVID-19 has the potential to complicate pre-existing chronic heart disease. Furthermore, there have been reports of de novo cardiac complications in individuals without any prior heart conditions. Interestingly, these cardiac abnormalities can occur independently, even in the absence of symptoms or signs of pneumonia. These observations emphasize the importance of monitoring cardiac health in individuals affected by COVID-19, both those with pre-existing heart conditions and those without, in order to

promptly identify and manage any potential cardiac complications [5, 6]. It is important to note that cutaneous manifestations can occur in both adults and children and can sometimes be the only symptom of COVID-19. Therefore, dermatological evaluations and awareness of these skin-related signs can contribute to early detection and appropriate management of the disease [7,8]. There is currently no definite classification of the dermatological manifestations in children and adult patients with COVID-19. However, the cutaneous manifestations can be divided into five main patterns: 1) maculopapular, 2) pseudopapular, 3) urtic, 4) vesicular-bullic, 5) livido, purpura, skin necrosis [9, 10, 11, 12, 13]. Skin manifestations may be reported in mildly symptomatic or asymptomatic patients as well as in patients with typical clinical signs of COVID-19 with a severe course [14]. Studies have indicated that approximately 10% of patients with COVID-19 may develop skin manifestations prior to the onset of respiratory symptoms. These skin manifestations can appear within a timeframe of 7 to 10 days after the diagnosis of COVID-19. This observation suggests that skin involvement may serve as an early indicator of the disease, even before the typical respiratory symptoms start to develop. Recognizing and monitoring of these skin manifestations can contribute to early detection, appropriate management, and reducing the spread of the virus [15].

The clinical manifestation of COVID-19 in infants and young children is milder, with infant mortality accounting for about 0.1% [16]. In the majority of cases, pediatric patients with COVID-19 tend to exhibit mild symptoms, often without fever or pneumonia. These mild symptoms can include cough, runny nose, sore throat, fatigue, and body aches. The recovery time for pediatric patients is generally estimated to be around 1-2 weeks after the onset of symptoms. It is important to note that each case is unique, and some children may experience more severe symptoms or complications. Regular monitoring, medical guidance, and appropriate care should be provided to ensure the well-being and recovery of pediatric patients with COVID-19 [17].The most common clinical manifestations in children include fever and cough; in some cases additional symptoms may be present, such as fatigue, myalgia, stuffy nose, runny nose, sneezing, sore throat, headache, vomiting, dizziness or abdominal pain [18,19]. In some cases in infected children, typical symptoms may be complicated, with gastrointestinal manifestations, Kawasaki-like illness and other cutaneous manifestations that can significantly delay the diagnosis of COVID-19 in children, potentially worsening their clinical outcomes [20]. In addition, the easing of quarantine requirements s led to the return of seasonal viral and bacterial infections, contributing to a more severe infection [21, 22]. In this regard, increased information on atypical forms of COVID-19 and an expanded panel of diagnostic tests for co-infections improve diagnostic algorithms and patient follow-up.

This article focuses on presenting clinical cases of an atypical course of COVID-19 in four hospitalized children aged from 11 months to 4 years and 9 months.

Materials and methods

The clinical research described in the article was approved by the local bioethical committee of Astana Medical University under approval number 6, dated January 31, 2022. The study was conducted in accordance with the principles outlined in the Helsinki Declaration of 1975 and its amendments from 2005, which ensure ethical guidelines for medical research involving human subjects. Written informed consent was obtained from the parents or guardians of the children participated in the study. Laboratory tests for hospitalized patients were conducted within the framework of standard protocol of diagnostics and treatment “Coronavirus infection in children”, approved by the Joint committee on quality of medical services of Ministry of Health of the Republic of Kazakhstan from “16” October 2020, Protocol №117.

Laboratory tests as part of the standard protocol

The diagnosis of COVID-19 was established by PCR testing using Intifica SARS-CoV-2 reagent kit for the detection of three RNA sites of coronavirus (SARS-CoV-2) by real-time RT-PCR method (AlkorBio, Russia) according to manufacturer’s instructions.

For all children hospitalized in MGDH №3, Astana, a general blood count was performed on a Nihon Kohden automatic haematology analyzer, Japan.

Additional investigations

For patients with gastrointestinal tract (GIT) lesions, co-program tests and testing for viral infections (rotavirus, enterovirus) were performed. Studies were performed using a reagent kit for detection of human rotavirus antigen “Rotavirus-antigen-IFA-BEST” No. FSR 2012/13864 (AO Vector-BEST, Russia). Bacteriological culture of stools for pathogenic and opportunistic microflora was performed by standard method with identification on automatic bacteriological analyzer “MASS Spectrometer” (BRUKER, USA). For patients with cutaneous manifestations immunoenzyme detection of M and G class immunoglobulins to Epstein-Barr virus capsid antigen in blood serum (plasma) using VECTOVEB-VCA-IgG test system № RZN 2017/5607 and VECTOVEB-

VCA-IgM RZN 2013/1279 (JSC Vektor-BEST, Russia) were performed.

For whole-genome sequencing of SARS-CoV-2 virus. RNA from nasopharyngeal swabs was obtained using the GeneJET Viral DNA and RNA Purification Kit (ThermoScientific, Lithuania) according to the manufacturer's instructions. The SARS-CoV-2 virus genome was amplified using the two primer pools included in the ARCTIC V4 panel. OT PCR was performed using BioMaster Premium reagent kit (Biolabmix, Russia). DNA libraries were prepared from PCR fragments covering the SARS-CoV-2 virus genome using the Nextera DNA Flex Library Prep Kit 96 samples (Cat. No. 20018704, Illumina, USA), according to the manufacturer's instructions. Sequencing was performed on a MiSeq sequencer platform (Illumina, USA) using MiSeq Reagent Kit v3, 600 Cycles (Catalog #MS-102-3003). Genome assembly was performed by mapping using the software BWA v0.7.17-r1188 [23]. Variant identification and consensus sequencing was performed using FreeBayes software [Richter F. et al. Whole genome de novo variant identification with FreeBayes and neural network approaches //bioRxiv. – 2020.] and BCFtools [24], respectively. Phylogenetic analysis and genotype determination of the SARS-CoV-2 virus genomes were performed using Nextstrain v 2.6.0 [25] and Pangolin v 4.1.2 [26], respectively.

Children were followed up using the ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) global surveillance protocol.

Results and discussion

Clinical cases, treatment and follow-up in the post-coVID period.

From 02 January 2023 to 02 February 2023, 37 children with the diagnosis of COVID-19 were treated at MGDH ¹ 3 in Astana. COVID-19 was confirmed by PCR testing. Most patients were young children (≤2 years). The most common clinical manifestations were nasopharyngitis, laryngitis, bronchitis, enteritis and febrile seizures. In addition to intoxication and catarrhal symptoms, 2 patients (4%) developed cutaneous manifestations and 15 (30.6%) had intestinal manifestations of infection. Common symptoms in patients with an atypical course of infection were fever with diurnal variation between 38.0 and 39.0°C and weakness. COVID-19 with skin lesions was observed in patients A and B.

Patient A, a female aged 1 year and 3 months, presented with a papulovesicular rash accompanied by itching on the face and extremities upon admission (Figure 1(a, b)). Further investigation using an enzyme immunoassay revealed a high titer of class M antibodies to the capsid protein of Epstein Barr virus, indicating acute infection. Additionally, the child exhibited eyelid and lower leg edema and reduced urine production. The general blood count conducted on the day of admission revealed an elevated platelet count of 511 × 10^9 g/l. The leukocyte count was within the normal range at 9.43 × 10^9/l, but there was a significant decrease in lymphocyte count, with an absolute lymphocyte count of 1.42 × 10^9 g/l, indicating lymphocytopenia. Monocytosis was also present, with a marked increase up to 15.9% (absolute count – 1.50 × 10^9/l). Based on these clinical and laboratory findings, the patient was diagnosed with concomitant pediatric papular acrodermatitis Gianotti-Crosti. The observed symptoms and laboratory abnormalities made it clear that this particular case was unique. Markers of inflammation were moderately elevated: C-reactive protein 5.6mg/l, erythrocyte sedimentation rate 15mm/hour and ferritin 141.79mcg/l. Dysproteinemia was also noted, with a decrease in total protein to 57.0 g/l and albumin to 40.2 g/l. Liver enzymes and renal function were within normal limits. Chest radiographs showed acute vascular and circulatory changes. No infiltrative focal lesions were seen.

Due to an increase in peripheral lymph nodes in the right cervical region, an ultrasound scan of the superficial lymph nodes was performed on the day 6th of admission, which showed an irregularly rounded, hypoechogenic, homogeneous lymph node with smooth, clear contours, measuring 10 mm. Conclusion – echo signs of lymphoadenitis in the infiltration stage.

In view of the increased pro-inflammatory markers, polymorphic, vesicular rash all over the body, as well as papular elements with purulent content in the limbs and buttocks, Zithmac (azithromycin) 2 was prescribed for antibacterial purposes, 5ml (200mg/5ml) 1 time a day, 6 days, with the antiallergic purpose received prednisolone 30mg (3mg/kg) as part of infusion therapy once, then with the antiallergic purpose received allergopressor therapy 2% by 0. 3ml intramuscularly once a day for 7 days. For detoxification, infusion therapy (sodium chloride 0.9%, 200 ml once daily for 2 days) was administered. Antiviral treatment was given with acyclovir 200mg once daily for 7 days, groprinosin 250mg/5ml oral 3.3ml 3 times daily for 4 days. Betamethasone ointment was used for local treatment. The child was hospitalised for a total of 8 days. On discharge, the skin was pale, the rash significantly reduced, secondary elements in the form of crusts, lymph nodes within normal limits, intoxication syndrome was controlled.

At the three-month follow-up, the child did not show any significant problems with sleep, appetite or physical activity. Two episodes of acute respiratory viral infection of moderate severity were observed. An increased allergic reaction compared to the period before the disease COVID-19, manifestations of atopic dermatitis in the form of a fine point rash when eating sugar-containing products, fruits (grapes, apricots) were noted. After the disease, mildly pigmented patches remained on the skin.

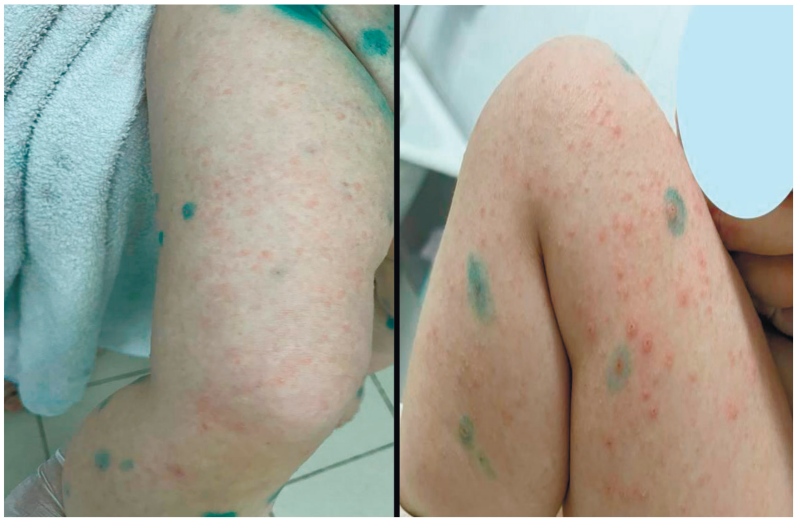

Figure 1(a, b) – Patient A with papulovesicular rash identified upon first admission

Patient B, a 4-year-old boy, presented with several symptoms on examination, a fever of 38.8ºC and a rash covering his entire body, including the face, back, scalp, extremities and groin. The rash was polymorphic, consisting of papules and vesicles. In addition, there were abundant papular eruptions with purulent content. The boy also had a hyperemic pharynx, suggesting inflammation, and vesicles in the paranasal sinuses, and with regard to respiratory symptoms, the patient had dyspnoea, suggesting dyspnoea. This finding suggests possible involvement of the respiratory system, which may have contributed to the dyspnoea. These clinical observations highlight the multifaceted nature of Patient B's symptoms, including the widespread rash, hyperemic pharynx and dyspnoea. Further diagnostic investigations and appropriate management strategies may be required to address these symptoms and provide appropriate treatment for the patient. According to the epidemiological data, the child was in contact with patients with varicella. At the time of admission, the child's condition was considered severe due to marked symptoms of general intoxication and skin syndrome. The diagnosis was: "Coronavirus infection, chickenpox, secondary infectious, severe. Allergy to herbal syrups. Delayed psycho-speech development (DPSD).

Blood tests showed monocytosis of 15.6% (abs. count) – 1.58 109/l, an accelerated erythrocyte sedimentation rate of 19 mm/hour, C-reactive protein was elevated to 9.2 mg/l. On the 3rd day of admission, procalcitonin increased to 0.250 ng/ml, with a further decrease to 0.096 ng/l on the 8th day.

The child was prescribed antiviral therapy with acyclovir (Acyclovir-ACOS 200 mg, tablets, orally) 5 p/day for 5 days. In view of the elevated levels of pro-inflammatory markers and the presence of secondary infectious elements with purulent contents, cefazolin 0.8 g intramuscularly 2 p/day for 6 days was administered for antibacterial purposes. For disinfection, the child received intravenous drip infusion therapy (sodium chloride 0.9%, infusion solution 150ml, glucose 5% 150ml) 1 p/day for the first 2 days. Allergopress 2%, 1ml, v/m 1 p/day for 3 days and Loratal 5mg orally 1 p/day for 4 days were given as antihistamines. The oral cavity, where vesicular eruptions were noted, was treated with 0.02% furacilin and betadine solutions 3 times daily for 5 days. The symptoms of intoxication, respiratory and catarrhal manifestations were relieved and body temperature normalised. At the time of discharge, the skin had a normal colour, the rash was crusted, and the hospital stay lasted 6 days.

Within 3 months of the illness, patient had a reduced appetite and therefore a lower than normal weight gain. The level of physical activity was slightly lower than before the illness, and sleep was not

disturbed. These symptoms gradually disappeared after 3 months. Frequent severe exacerbations of atopic dermatitis occurred 2 times in 3 months.

Patients B and D had COVID-19 with gastrointestinal manifestations.

Patient C, an 11-month-old boy, presented with several symptoms on admission. He complained of vomiting, liquid stools, weakness and loss of appetite. The severity of his condition was attributed to symptoms of intoxication and toxicosis with dehydration (excicosis) of grade 1. On admission he had a fever of 39ºC. Laboratory results on the day of admission showed a decrease in haemoglobin to 108 g/l, while erythrocyte and haematocrit values remained within the normal range. There was a notable lymphocytosis of 68.4%, indicating an increase in the number of lymphocytes, and a monocytosis of 11%, indicating an increased number of monocytes. The urinalysis showed the presence of ketones at a concentration of 5 mmol/l and protein at a concentration of 0.15 g/l. The presence of ketones in the urine indicates a state of ketosis, which can occur due to increased breakdown of fatty acids for energy. The presence of protein in the urine may indicate renal involvement or inflammation.

Overall, the clinical presentation and laboratory findings in patient B suggest a severe case of gastrointestinal infection, possibly viral in nature. The symptoms of vomiting, liquid stools, weakness and decreased appetite, together with the laboratory abnormalities, provide valuable information for the appropriate management and treatment of the patient's condition, including rehydration and supportive care.

A bacteriological examination of the stool showed an increase in Proteus mirabilis (1*10^5 CFU, /ml). The child was diagnosed with coronavirus infection, mild anaemia and acute intestinal infection (AKI).

The child was treated: sodium chloride infusion solution 0.9% 110ml, glucose solution 10% 110ml, ascorbic acid 5%, 1 ml, intravenously (drip) 2 p/day to replenish fluid loss. 2 days. Regidron powder for oral solution, orally 1 p/day, 1 day.

The patient's condition improved, and at the insistence of the parents, the child was discharged to the outpatient clinic, where dietary advice, enzyme therapy and probiotics were given.

At the three-month follow-up after SARS-COV-2 infection, the child showed no sleep, appetite or physical activity. He had mild to moderate acute respiratory viral infection, conjunctivitis and persistent signs of anaemia.

Patient D, a boy aged 1 year and 9 months presented with multiple symptoms on admission. He complained of general weakness, lethargy, decreased appetite, nausea, frequent liquid stools and had a temperature of 38.6ºC. The severity of his condition was attributed to intoxication syndrome and toxicosis with dehydration (excicosis). The general blood test showed an increase in the leukocyte count to 13.25 × 10^9/l, indicating leukocytosis. In addition, the erythrocyte sedimentation rate was accelerated to 21 mm/hour, suggesting an inflammatory response. The lymphocyte count was elevated, with lymphocytosis reaching 54.9%. Further diagnostic tests were performed, specifically a faecal enzyme immunoassay, which was positive for rotavirus antigen. This confirmed the presence of rotavirus infection as the cause of the symptoms and clinical presentation. The combination of symptoms, including generalised weakness, gastrointestinal upset, fever and laboratory findings of leukocytosis, elevated erythrocyte sedimentation rate and lymphocytosis, supports the diagnosis of severe rotavirus infection in this young boy. Prompt treatment and supportive care, including rehydration and symptomatic treatment, may be necessary to relieve symptoms and facilitate recovery.

He received disinfection and rehydration therapy: Rehydron – powder for preparation of oral solution, orally 1 day a week for 6 days, glucose solution 10% 200 ml, ascorbic acid 5%, 1 ml, sodium chloride 0.9% 120 ml intravenously (drip) – 1 day a week for 3 days. Inhalation with sodium chloride 3% solution 2 ml 3 times a day for 5 days. Cefuroxime 650mg intramuscularly 2 times a day for 5 days for antibacterial purposes. The child's condition improved and the symptoms of intoxication were relieved. The child was hospitalised for 8 days.

In a pandemic, any infectious clinical condition requires first and foremost the exclusion of COVID-19 infection. In this situation, the existence of other "traditional" infectious agents that are also highly contagious and have a wide range of clinical features is sometimes forgotten. The atypical forms of coronavirus infection in children described by us were aggravated by concomitant infectious diseases, the main clinical features of which were skin lesions and a pattern of intestinal infection.

In many publications on the diversity of COVID-19 in patients of different ages, co-infections with other viruses and bacteria have been reported. For example, in a metagenomic data analysis using the Illumina NextSeq 500 platform, genetic material from respiratory viruses was detected in 25% of all samples from patients infected with SARS-CoV-2, while human viruses other than SARS-CoV-2 were detected in 80% of them (Anneloviridae, Cycloviridae, Rotavirus A, Measles morbillivirus, Alphapapilomavirus) [27]. There is very little information on co-infection with Epstein-Barr virus (EBV) and

SARS CoV-2. The case history of a 19-year-old French woman with two days of fever, bilateral eyelid oedema and oedema of the right side of the face is described. In addition to the cutaneous manifestations, physical examination revealed bilateral cervical lymphadenopathy, non-pulmonary pharyngotonsillitis and splenomegaly. Laboratory tests revealed the presence of SARS-CoV-2 RNA (OT-PCR) and EBV (PCR) [28]. A study by Ting Chen et al. showed that patients with COVID-19 have a high incidence of EBV co-infection. It was found that EBV reactivation may be associated with the severity of COVID-19 [29]. Other researchers have suggested that the presence of SARS-CoV-2 provides a favourable background for EBV infection [30]. Co-infection with both COVID-19 and varicella has been reported, resulting in pleuropneumonia in a 10-month-old child. The association between COVID-19 and varicella is suggested by the authors as a potentially dangerous situation in children [31]. Described clinical cases of co-infection with varicella (chickenpox) and COVID-19 in an adolescent and in a 5-year-old child [32,33]. Early identification of co-infection with varicella-zoster virus and SARS-CoV-2 in a 20-year-old patient in Spain allowed optimal treatment to halt progression of lung damage and reduce the likelihood of death, which would not have been possible if we had suspected SARS-CoV-2 infection alone [34]. In co-infection, herpes zoster reactivation is known to be the main marker of COVID-19, there is a synergy between both viruses causing immune status abnormalities in patients [35]. The description of some clinical cases in children mentions possible reactivation of herpesvirus infections associated with SARS-CoV-2 [36]. A retrospective analysis of stool samples from children admitted to an infectious disease hospital with acute enteric infection is reported. SARS-CoV-2 RNA was detected in 5 samples in combination with norovirus RNA, in 1 sample with rotavirus RNA and in another case with adenovirus DNA. Coronavirus was identified in 2 samples in combination with rotavirus/norovirus and norovirus/adenovirus [37].

As indicated in literature review, co-infection with covid and post-covid viruses is quite common, raising the question of the need to adapt and optimise existing designs of post-covid surveillance programmes.

Whole Genome Sequencing and Phylogenetic Analysis

For SARS2-94, SARS2-122, SARS2-154 and SARS2-144 samples, 298824, 277726, 232142 and 297170 reads were obtained, respectively. The average sequencing depth was 2496×.

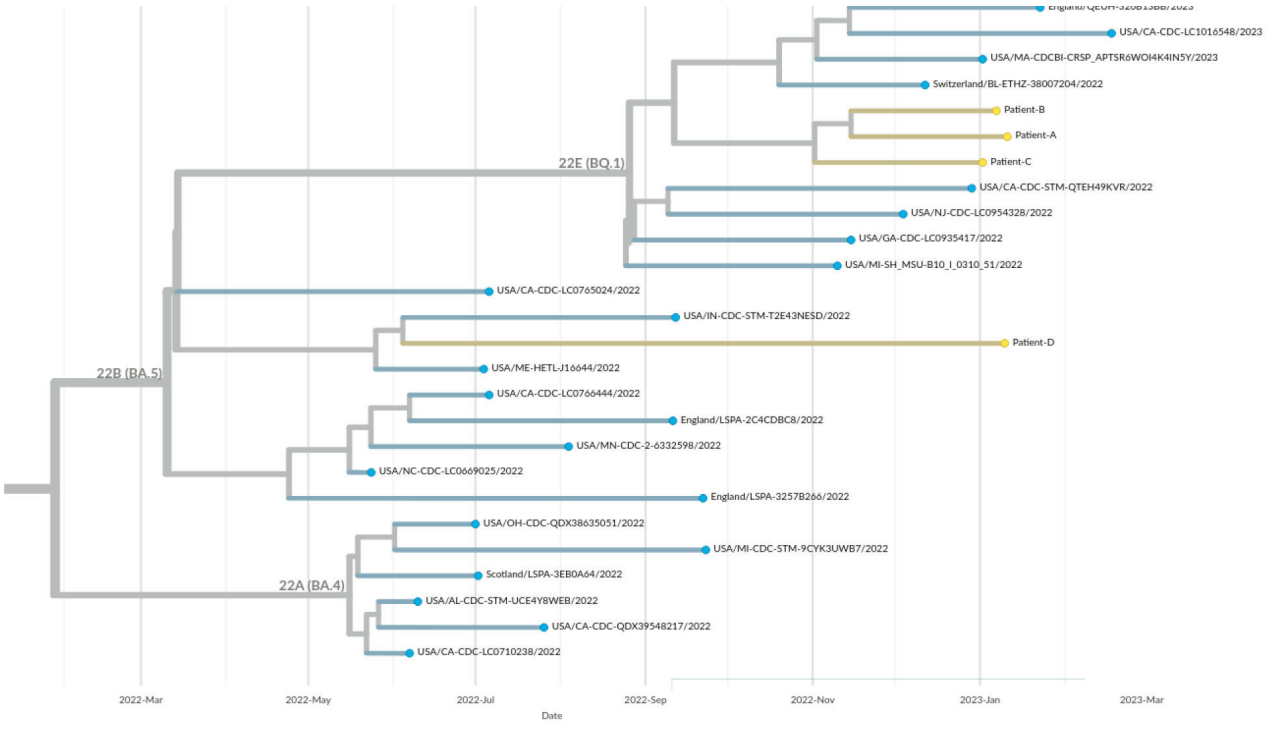

Figure 2 – below shows the phylogenetic tree reconstructed.

According to the genotyping results of the Nextstrain and Pangolin systems, all 4 samples belong to the Omicron lineage 22E: Patient-A, Patient-B and Patient-C. As shown in the figure, the Patient-D isolate belongs to branch 22B. The remaining 3 isolates (SARS2-144, SARS2-154 and SARS2-94) are clustered on the daughter branch 22E.

In an extensive study of patient samples from Astana, August 2021-May 2022, phylogenetic analysis of 341 samples showed that 205 genomes (60.1%) clustered under the 21K (Omicron) clade, 131 genomes (38.4%) clustered under the 21J (Delta) clade [38]. The clustering of the genomes we studied under the omicron clade suggests that the genotypes identified belong to the dominant group and that there is no relationship between genotype and clinical manifestation.

Although a large database exists, the clinical characteristics of COVID-19 are not yet fully understood, including its cutaneous manifestations. Despite associations of cutaneous manifestations with some respiratory viruses that were previously described [39], these cases are not characteristic of the coronavirus family [40]. In this situation, additional knowledge of the morphological changes in the skin in COVID-19 may help not only to diagnose the disease, but also to treat the infection more successfully.

Conclusions

The COVID-19 pandemic has imposed an unprecedented economic and public health burden. It has also had a deleterious effect, increasing morbidity and mortality through systemic damage as a manifestation of the body's systemic inflammatory response to infection. Physicians should remain vigilant when assessing pediatric (and adult) patients who may initially present to a dermatology department or emergency department with COVID19 presenting as a rash and AII.

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