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BRIEF REPORT

Fatal Measles Virus Infection After Rituximab-Containing Chemotherapy in a Previously Vaccinated Patient

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We report the case of a young patient treated with rituximab-containing chemotherapy who was infected with measles despite previous vaccination. Treatment with vitamin A, ribavirin, and immunoglobulins was started; nevertheless he developed severe pneumonitis and deceased. Broad vaccination coverage is crucial in protecting vulnerable subjects.

Keywords. immunocompromised; measles; rituximab; vaccination.

CASE PRESENTATION

We present the case of a 26-year-old man who was hospitalized with fever and neutropenia. He was known to have chronic lymphocytic leukemia (CLL; small lymphocytic lymphoma, low risk, Binet stade B, Rai II; 11q deletion, no TP53 mutation), diagnosed 7 months before admission, and had been treated with 7 cycles of chemotherapy with fludarabine, cyclophosphamide, and rituximab until 1 month before admission. He had been receiving *Pneumocystis* pneumonia prophylaxis with trimethoprim/sulfamethoxazole and herpes simplex virus prophylaxis with valaciclovir. There was no recent travel history, no known animal contact, no recent sexual risk exposure, and no known infectious disease in close contacts. Vaccinations had been completed according to Swiss national recommendations, including 2 documented measles, mumps, and rubella (MMR) vaccine doses in 1993 and 1999.

At hospital entry, the patient reported sore throat, unproductive cough, and fever without chills since 1 day before admission. The clinical exam was only remarkable for pharyngitis and the previously known cervical lymphadenopathy. C-reactive protein was moderately elevated (53 mg/L). The patient was thrombocytopenic (73 G/L) and had a leukocytopenia (1.08 G/L; 0.67 G/L neutrophile granulocytes). A chest x-ray showed no infiltrates, and a rapid-antigen detection test for group A streptococci from a throat swab was negative.

Empirical treatment with cefepime was started. Blood cultures and multiplex polymerase chain reaction (PCR) for respiratory viruses using a nasopharyngeal swab remained negative. Four days after symptom onset, the patient developed a confluent maculopapular rash of the face and upper trunk. Skin biopsy showed a perivascular lymphohistiocytic infiltrate and necrotic keratinocytes—changes compatible with an exanthematous drug eruption. For this reason, trimethoprim/sulfamethoxazole was stopped, and cefepime was switched to meropenem.

Besides a progressive craniocaudal evolution of the maculopapular rash (Figure 1B), the patient developed ulcerative stomatitis compatible with Koplik spots (Figure 1A) and bilateral conjunctivitis on day 7 after symptom onset. These findings raised the suspicion of a measles virus infection, although the patient had been vaccinated as a child, as previously described. Positive measles real-time PCR from a throat swab confirmed the suspected diagnosis. In the month before, there had been no measles outbreaks in the patient's region of residence, and he was not aware of any contact with a measles-infected individual. Measles IgG and IgM (Serion ELISA classic, Virion/Serion GmbH, Würzburg, Germany) and rubella virus IgG were negative on day 6 after symptom onset, and mumps virus IgG was borderline positive (93 U/mL; cutoff, 70 U/mL), despite documented prior vaccination with 2 doses. Total IgG was in the lower normal range (8.6 G/L; normal range, 7–16 G/L).

Treatment with intravenous ribavirin, intravenous immunoglobulins, and vitamin A was started. On day 8 after symptom onset, the patient developed progressive dyspnea and hypoxia in addition to the unproductive cough, while the fever persisted. A chest computed tomography scan showed bilateral, in part nodular pulmonary consolidations with adjacent ground glass infiltrations, compatible with pneumonitis (Figure 1C). Elevated transaminases up to 2 to 3 times the upper norm were observed as well. On day 15, he fulfilled the definition of acute respiratory distress syndrome (ARDS) and required invasive ventilation, and on the following day veno-venous extracorporeal membrane oxygenation (VV-ECMO). On day 17 after the onset of symptoms, the patient developed venous bleeding at the puncture site of the VV-ECMO and succumbed to mixed shock and severe pneumonitis.

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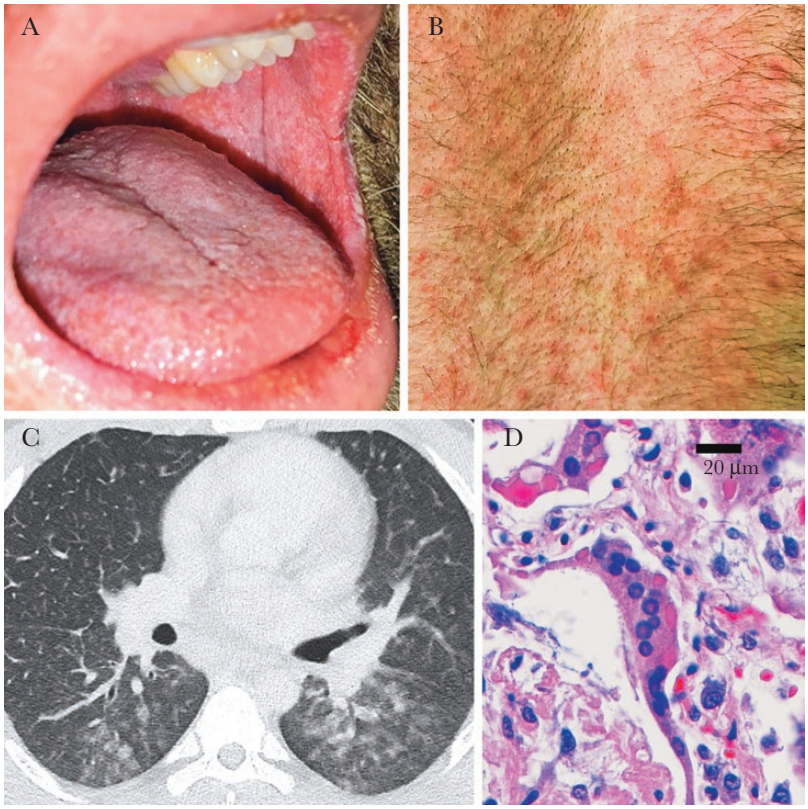

Figure 1. A, Enanthema, no scale available. B, Maculopapular rash (back of the patient), no scale available. C, Computed tomography lung scan with nodular peribronchial infiltrates. D, Histology of the lung section (hematoxylin and eosin stain, 80× magnification) of the patient. Giant cell pneumonitis: numerous syncytial multinuclear giant cells with intracytoplasmic and intranuclear inclusions lining the alveolar walls, with a background of diffuse alveolar damage.

Postmortem examination showed macroscopically severe diffuse micronodular parenchymal consolidations of the lungs. Apart from the aspect of a diffuse alveolar damage, correlating with the clinical picture of ARDS, histology revealed numerous syncytial multinuclear giant cells with intracytoplasmic and intranuclear inclusions lining the alveolar walls, consistent with measles pneumonitis (Figure 1D).

DISCUSSION

The presented case demonstrates the severity of measles infections in immunocompromised patients and highlights the importance of herd immunity, as rituximab can compromise previously acquired humoral immunity.

Measles in immunocompromised patients bears serious complications in about 80% of cases. Pneumonitis is the principal complication, accounting for most measles-associated deaths [1]. Clinical presentation in immunocompromised patients frequently is atypical, with 27%–40% of patients presenting without a rash [1].

Humoral immunity plays the main role in preventing measles virus infection, with neutralizing antibody titers at the time of exposure correlating with protection from disease [2]. In our patient, a serum sample from before the start of rituximab was not available, but he had received 2 documented MMR vaccine doses before his infection, which induces long-lasting protection in 97% of vaccinated subjects [3]. However, at the time of diagnosis, he had no measurable antibodies to measles or rubella, and he had borderline mumps IgG. We assume this is due to his rituximab-containing chemotherapy. Additionally, the patient's underlying disease may have played a role in his vulnerability, although pretreatment hypogammaglobulinemia in CLL is far less commonly seen than after treatment with rituximab [4]. Rituximab, a monoclonal CD-20 antibody, is known to induce transient hypogammaglobulinemia in 39% of patients [5]. After application of rituximab, the immune response to recall antigens is reduced [6]. Additionally, fludarabine, in addition to its effect on T-lymphocytes, also leads to prominent B-cell depletion [7]; the combination of fludarabine with rituximab has been independently associated with higher infection rates [8]. A primary vaccine failure cannot be ruled out as an explanation for the missing immunity against measles; however, it is a far less probable explanation given the vaccine's high 2-dose effectiveness and the multiple reasons for humoral immunodeficiency depicted above.

Immune control of measles infection is primarily dependent on T-lymphocyte cytolytic response, whereas humoral immunity seems to play only a minor role in disease control. B-lymphocyte-depleted rhesus monkeys have a clinical and

virological course of measles infection that is indistinguishable from that of healthy monkeys [9]. Children with hypogammaglobinemia have a normal disease course, in contrast to children with cellular immune defects [1, 10], in whom measles infection is associated with a high risk of complications. Mainly the T-lymphocyte cytolytic response is associated with clearance of infection [11]. In our patient, the T-lymphocyte cytolytic response was heavily compromised due to chemotherapy with fludarabine and cyclophosphamide.

Evidence on treatment options in severe measles infection is limited. Management consists primarily of supportive therapy and treatment of secondary bacterial infections.

Ribavirin, a ribosyl purine analogue, shows in vitro activity against measles virus [12]. One nonblinded randomized trial with ribavirin vs supportive therapy in 100 nonimmunocompromised patients found a reduced time to resolution of fever with ribavirin (mean, 7.3 vs 3.2 days). Furthermore, in the ribavirin group, there were no complications vs 11% with respiratory symptoms, 2% with encephalitis, and 2% with a fatal outcome in the control group [13]. The use of intravenous or aerosolized ribavirin in severe measles infection in immunocompromised patients has also been reported in a few case reports and series, but a significant survival benefit could not be proven in these series [1]. One case series [14] found significantly higher mortality in pediatric oncologic patients with measles infection if ribavirin application was delayed, but the observation was based on only 2 patients with a fatal outcome.

Reduced mortality and major complications after oral application of vitamin A in children with measles infection have been demonstrated in several randomized controlled trials in third world or developing countries [15]. It is unclear if this effect is transferable to immunocompromised patients in populations with a lower prevalence of vitamin A deficiency. Nevertheless, in most case series of severe measles infection, the patients have received oral vitamin A.

The use of intravenous immunoglobulins in severe measles infection in immunocompromised patients is common, but there is no evidence of its ability to improve the disease course. On the other side, its effect as postexposure prophylaxis is well established. Given the limited role of humoral immunity in disease control (see further up), a relevant benefit of intravenous immunoglobulin administration for a therapeutic indication in measles is improbable.

Given the fact that therapeutic options in severe measles infection are limited, as described above, the role of herd immunity to protect vulnerable (eg, immunocompromised, children younger than age 1 year) subjects is crucial. A recent drop in vaccination coverage in Europe, with 2-vaccine-dose coverage below the World Health Organization (WHO) herd immunity threshold of 95% in 20 of 27 reporting countries, led to an epidemic of more than 14 000 cases, including 30 fatal ones in 2017. MMR 1-dose coverage in the United States is still below the WHO herd immunity threshold, with local variation. In this epidemiologic situation of limited herd immunity, a cocooning vaccination strategy should be envisaged, namely to vaccinate people with close contact to patients whose immunosuppressive therapy is hampering their vaccination protection.

CONCLUSIONS

Measles virus infections in immunocompromised patients often have an atypical presentation and can even occur in previously vaccinated individuals (eg, after rituximab), as shown in this case presentation. Given the limited therapeutic options, herd immunity, namely high immunization coverage and a cocooning strategy, is crucial to the protection of vulnerable subjects. Ongoing efforts to raise confidence in vaccines and increase population immunity should be intensified.

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