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Case report

Yellow fever vaccine-associated neurotropic disease (YEL-AND) – A case report

Jolanta Florczak-Wyspiańska *, *Ewa Nawotczyńska*, *Wojciech Kozubski*

Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland

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ABSTRACT

Yellow fever (YF) is a mosquito-borne viral hemorrhagic fever, which is a serious and potentially fatal disease with no specific antiviral treatment that can be effectively prevented by an attenuated vaccine (YEL). Despite the long history of safe and efficacious YF vaccination, sporadic case reports of serious adverse events (SAEs) have been reported, including yellow fever vaccine-associated neurotropic disease (YEL-AND). YEL-AND usually appears within one month of YF vaccination, manifesting as meningoencephalitis, Guillain–Barré syndrome (GBS) or acute disseminated encephalomyelitis (ADEM). We report a case of YEL-AND with meningitis presentation in a 39-year-old Caucasian man without evidence of significant risk factors, which was confirmed by the presence of the YF virus and specific immunoglobulin G (IgG) antibodies in the cerebrospinal fluid (CSF). In conclusion, we should stress the importance of balancing the risk of SAEs associated with the vaccine and the benefits of YF vaccination for each patient individually.

1. Introduction

Yellow fever (YF) is a viral hemorrhagic fever, which is a vector-borne disease resulting from transmission of the yellow fever virus (YFV) to a human from the bite of an infected mosquito, *Aedes* or *Haemagogus* species [1,2]. YFV is a single-stranded ribonucleic acid (RNA) virus that belongs to the genus *Flavivirus* [1,2]. YF is endemic to sub-Saharan Africa and tropical South America and is estimated to cause 200,000 cases of clinical disease and 30,000 deaths annually [1,2]. Clinically, the disease varies from a mild, undifferentiated febrile illness to a severe disease with jaundice, hemorrhagic manifestation and hepatorenal failure marked by a case-fatality ratio of 20–50% [1–3]. Differences in viral strains and host immune factors are probably responsible for the range of clinical symptoms [1]. Because no specific antiviral treatment exists for YF, prevention is critical to lower disease morbidity and mortality. All residents and travelers to areas in which YF is endemic should be warned of the risk of contracting the disease and should be advised about available preventive measures [2]. Immunization, supplemented with prevention of mosquito bites, is now the most important method of YF prevention [1]. Vaccines against YF have been available since the 1940s and are responsible for a significant reduction of disease occurrence [1,4].

* *Corresponding author at*: Department of Neurology, Poznan University of Medical Sciences, Przybyszewskiego 49 St., 60-355 Poznan, Poland. Tel.: +48 61 8691 454; fax: +48 61 8691 697.
E-mail address: jolaflorczak@op.pl (J. Florczak-Wyspiańska).
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All current YF vaccines derive from the 17D strain: 17DD and 17D-204 [1,2]. The live attenuated YF vaccine (YEL) is one of the safest and most efficacious vaccines ever made [5]. Seroconversion occurs in >95% of recipients by 10 days after vaccination [2,5]. According to the World Health Organization's (WHO) International Health Regulations (IHRs), the certificate of immunization for travelers is valid for 10 years after the most recent YF vaccination [4]. Neutralizing antibodies (NAs) against YFV, estimated by means of a plaque reduction neutralization test (PRNT), are considered to be the best surrogate marker for protection against YF [4,6]. Despite a long history of safe and efficacious YF vaccination, sporadic cases of serious adverse events (SAEs) have been reported, including severe allergic reactions, neurotropic disease (yellow-fever vaccine-associated neurotropic disease, YEL-AND) and viscerotropic disease (yellow-fever vaccine-associated viscerotropic disease, YEL-AVD) [3,4]. The last one is especially notable for its lethality [7]. YEL-AVD is an acute multi-organ dysfunction resembling a fulminant infection by wild-type YFV, with manifestations that include fever, jaundice, hepatitis, renal failure, thrombocytopenia, bleeding dyscrasia and respiratory failure [8]. Incidence of YEL-AVD is approximately 0.4 per 100,000 doses of vaccine administered, and the case-fatality ratio is estimated at 65% [2,9,11]. YEL-AND appears typically within one month after YF vaccination, manifesting itself as meningoencephalitis, Guillain–Barré syndrome (GBS) or acute disseminated encephalomyelitis (ADEM) [2,10]. Its estimated incidence is 0.4–0.8 per 100,000 doses administered [2,9,11]. Although the majority of patients recover without sequelae [1–3], a few reports of fatal YEL-AND have been published [5,8,10]. The meningoencephalitis cases were considered to definitely have been caused by the YF vaccine if 17D-204 YFV was isolated from the cerebrospinal fluid (CSF) and/or 17D-204 YFV RNA was amplified from CSF by nucleic acid-amplification testing (for example RT-PCR, reverse-transcription polymerase chain reaction), or the YFV-specific immunoglobulin M (IgM) antibody was found in CSF by IgM-capture ELISA [2,5,10]. ADEM and GBS are thought to be associated with autoimmune mechanisms in which pathogenic autoantibodies are generated in response to an antecedent stimulus [2,10].

The YF vaccine is contraindicated in several situations, e.g. in allergy to YF vaccine components, age <6 months, symptomatic human immunodeficiency virus (HIV) infection or CD4 T-lymphocyte count <200 cells/mm^3, thymus disorders associated with abnormal immune cell function, primary immunodeficiency, malignant neoplasm, organ transplantation, and immunosuppressive or immunomodulatory therapy [2,4]. Precautions for its use include an age of 6–8 months, an age over 60 years, asymptomatic HIV infection and a CD4 T-lymphocyte count of 200–499 cells/mm^3, pregnancy and breast-feeding [2,3,12].

One of the vaccines available against YF is the live, attenuated, 17D-204 vaccine Stamaril® (Sanofi, Pasteur, France), which is available in more than 100 countries, including in Europe, with a licence since 1983 [3]. In the last 20 years of pharmacovigilance surveillance, only six cases of definite YEL-AND have been reported worldwide following Stamaril® vaccination for approximately 392 million doses distributed [3]. Since marketing authorization in 1996, approximately 236,000 doses of the Stamaril® vaccine have been distributed in Poland, and a total of 3 cases of SAEs as per international recommendations [13], has been reported in Poland.

2. Case report

A 39-year-old Caucasian man was admitted to the neurological ward due to severe headache, malaise and increasing fever for a few days ranging from 37.5 to 39 °C. Two weeks before admission the patient had been vaccinated against YF with Stamaril® for the first time in his life due to a planned journey to Panama. The above-mentioned symptoms commenced five days after the vaccination. There was also a history of frequent sinusitis, and the last infection had taken place one month before the YF vaccination. Generally, the patient was in good health, without chronic illnesses, including thymus disorders and primary immunodeficiency, or any necessity of chronic treatment. On admission, the patient's neurological examination, basic laboratory tests of blood and urine, X-ray of the chest and paranasal sinuses, electroencephalography (EEG) as well as computerized tomography (CT) of the head showed no abnormalities. The CSF examination revealed lymphocytic cytosis, 448 cells per mm^3, while the protein and glucose concentrations were within normal limits, and oligoclonal bands were absent. Based on the clinical picture and CSF examination, the diagnosis of meningitis was made and empiric therapy with acyclovir and ceftriaxone was started. On the second day of hospitalization, signs of a stiff neck, hyperreflexia and pain in the cervical and thoracic region of the vertebral column appeared. Magnetic resonance imaging (MRI) studies of the brain, cervical and thoracic spinal cord were ordered and, except for intensive meningeal contrast enhancement in the cervical localization, no abnormalities were found. Ultrasonography (USG) of the abdomen, CT of the chest and abdomen were all within normal limits. Subsequent extensive investigations from the blood, urine and CSF for infection (bacteria, fungi and viruses, including HIV) were all negative with the exception of YF. The analyses of serum and CSF samples performed on the 20th and 15th day post-vaccination for YFV by RT-PCR were negative in the serum and positive in CSF. Moreover, the results obtained on the 20th day post-vaccination were negative for the presence of specific IgM and IgG antibodies in CSF while positive for both classes of antibodies in the serum (see Table 1). On the 7th day after admission, due to a worsening of the patient's clinical status, with fever up to 39.9 °C and severe headache, intravenous immunoglobulin (IVIG, 0.4 g/kg/day) therapy was introduced for three days with good effect. Subsequently, empiric therapy was stopped and only supportive therapy was continued. The control lumbar puncture performed on the 19th day of hospitalization (32nd day post-vaccination) revealed a significant decrease in cytosis to 23 cells/mm^3, with normal glucose and protein concentrations. Control analyses of serum, CSF and urine for YFV, and specific IgM and IgG antibodies in the serum and CSF were conducted, revealing the presence of IgG antibodies in the serum and in CSF (see Table 1). In the meantime, a transient yet significant increase of liver enzymes was observed. A number of diagnostic procedures as well as

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