CASE REPORT

Inadvertent yellow fever vaccination of a patient with Crohn's disease treated with infliximab and methotrexate

Christina Ekenberg,[1] Nina Friis-Møller,[1] Thomas Ulstrup,[2] Claus Aalykke[2]

[1]Department of Infectious Diseases, Odense University Hospital, Odense C, Denmark
[2]Section of Gastroenterology, Department of Medicine, Svendborg Hospital, Svendborg, Denmark

Correspondence to
Christina Ekenberg,
christina.ekenberg@regionh.dk

Accepted 13 August 2016

SUMMARY

We present a case of a 56-year-old woman with Crohn's disease, treated with methotrexate and infliximab, who inadvertently received yellow fever vaccination (YFV) prior to a journey to Tanzania. She was not previously vaccinated against YF. YFV contains live-attenuated virus, and is contraindicated in patients treated with immunosuppressive drugs. Following vaccination, the patient fell ill with influenza-like illness. Elevated transaminase levels and YF viremia were detected. Despite being immunocompromised, the patient did not develop more severe adverse effects. Neutralising antibodies to YF virus were detected on day 14 following vaccination and remained protective at least 10 months after vaccination. Limited data is available on outcomes of YFV in patients receiving immunosuppressive therapy, including biologics, and we report this case as a reminder of vigilance of vaccine recommendations in this population.

BACKGROUND

Inflammatory bowel disease (IBD), that is, Crohn's disease and ulcerative colitis, often debuts in younger adults, and the course of the disease is lifelong.[1] In moderate to severe active Crohn's disease combination therapy with biologics and other immunosuppressive drugs is often used.

The side effects to biologics including infliximab (IFX) include increased susceptibility to and possible reactivation of dormant infections. To countermeasure these occurrences there are national and international guidelines for the screening of dormant infections and vaccination programmes.[2 3] Owing to the mechanisms of action of immunosuppressives, including biologics, the use of live-attenuated vaccines is contraindicated during therapy. Owing to the half-life of the drugs, cessation of biologics such as IFX has to be performed at least 3–6 months prior to the use of a live-attenuated vaccine including yellow fever vaccination (YFV).[2–4] Having high immunogenic and thus preventive potential in healthy individuals, live-attenuated vaccines may possess a great risk in people with impaired immune system.

CASE PRESENTATION

A 56-year-old woman with IBD for almost 30 years was originally considered having ulcerative colitis.

Owing to the several clinically significant exacerbations, prednisolone treatment was used for longer periods of time in addition to sulfasalazine and mesalazine. Owing to steroid dependency, azathioprine was introduced; however, this resulted in significant drug-induced liver injury (DILI) and was therefore subsequently withdrawn.

Between 2009 and 2012, the patient did not receive any medical treatment for her IBD, and she was not seen in the gastroenterology outpatient clinic. Eventually she relapsed, and a colonoscopy was performed, showing ulcerations in the transverse, descending and sigmoid colon, whereas the mucosa in the right-sided colon and rectum was normal. Histology showed acute and chronic inflammation with some crypt distortion including a single epithelioid granuloma. Mesalazine treatment was resumed, and the patient went into clinical remission.

In 2013, she had a large perianal abscess treated conservatively with antibiotics followed by spontaneous depletion. In 2014, the patient experienced a severe relapse with abdominal pain, non-bloody diarrhoea and high fever despite mesalazine treatment. Sigmoidoscopy showed inflamed mucosa with deep ulcerations above the rectosigmoid transition zone, and the patient was treated with high doses of parenteral glucocorticoid and once again went into clinical remission.

In 2014, a normal video capsule endoscopy of the small intestine was performed, and the patient's IBD was reclassified to steroid-dependent colonic Crohn's disease. Prednisolone was tapered and mercaptopurine treatment was introduced. However, DILI developed again and mercaptopurin was withdrawn.

A rising faecal calprotectin to 559 mg/kg (normal range: <50 mg/kg) after the withdrawal of prednisolone suggested a forthcoming relapse, and taking into consideration that the patient had documented steroid-induced osteoporosis and diabetes, prophylactic treatment with methotrexate (MTX) 25 mg subcutaneously (SC) once a week in combination with IFX 400 mg intravenously at week 0, 2, 6 and subsequently every 8 weeks was started in November 2014. The combination treatment was well tolerated, and after 3 months of treatment, clinical remission was obtained which was supported by an almost normal faecal calprotectin of 72 mg/kg.

Despite the long course of disease involving several exacerbations, no surgical resections had been performed.

On 13 March 2015, prior to a forthcoming holiday in Zanzibar, Tanzania, the patient saw her general practitioner for vaccine counselling. Despite treatment with MTX, and the latest IFX

To cite: Ekenberg C, Friis-Møller N, Ulstrup T, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2016-215403

infusion given on 9 February, the patient inadvertently received YFV 0.5 mL SC (Stamaril, Sanofi Pasteur MSD). No other vaccinations were given. The inadvertent vaccination was realised shortly after, and the patient's immunosuppressive treatment was stopped immediately.

Six days after the YFV, the patient developed influenza-like symptoms with high fever of 40°C, severe headache and general weakness approximately for 1 week suggestive of an adverse vaccine effect. The patient did not show any signs of jaundice or other liver failure symptoms, and no treatment was initiated.

All laboratory tests were normal including C reactive protein, except a slightly elevated alanine aminotransferase (ALT) of 125 U/L (normal adult female range: 0–45 U/L) increasing to a maximum of 180 U/L 6 days after the vaccination. Prior to vaccination ALT levels had been fluctuating with a maximum level of 117 U/L.

Two days after the YFV, the PCR of serum specimen for YF viral RNA was negative (table 1). After 6 days, PCR showed detectable levels of YF viral RNA consistent with the patient's symptoms and after 14 days, serological tests showed, in addition to continuous YF viremia, the presence of YF-neutralising antibodies with positive IgM and IgG antibody titres of 1:80 and 1:320, respectively. Apart from suffering from fatigue, the patient recovered completely, and her condition did not require hospitalisation.

OUTCOME AND FOLLOW-UP

Four weeks after the YFV another IFX infusion was given. At that time, the patient had developed protective antibodies with an IgG titre of 1:320, and she did not have any adverse events. At 6 weeks, no more viremia was detected and after 3 months, YF-neutralising antibodies were still present with an IgG antibody titre of 1:640 (table 1).

The sero-protection persisted up to 10 months after YFV. At that time, additional serological status was assessed prior to a holiday in Ghana, where YF vaccination is required (table 1). Furthermore, the patient's Crohn's disease has remained in clinical remission for more than a year, including after the withdrawal of IFX and ongoing MTX monotherapy.

DISCUSSION

We have presented a case that describes a benign postvaccination course in a patient undergoing immunosuppressive treatment with IFX and MTX. YF virus is an RNA virus that belongs to the group of Flavi virus. It is transmitted to humans through infected mosquitos. YF can range in severity from a mild febrile illness to severe disease with jaundice and haemorrhage; the case-fatality ratio for severe YF disease is 20-50%.[5] An estimated 200 000 YF cases occur worldwide annually, with ~87% in Africa. There is no specific treatment, but infection can be prevented by vaccination.[6] YF vaccine is recommended for people aged ≥9 months who are travelling to or living in areas with risk of YF virus transmission,[6] and proof of YFV can be required for entry into certain countries. However, YF vaccine is contraindicated for people whose immunological response is suppressed by drugs because of presumed increased risk of YFV-associated serious adverse events (SAEs).[6]

The YF vaccine is considered one of the safest and most effective vaccines. Worldwide more than 600 million vaccines have been administered. The vaccine is highly effective since protective antibodies develop in 99% of recipients within 30 days after vaccination. In addition, only mild adverse events are reported in 10–20% of recipients.[7] In immunocompromised patients, however, YF vaccination can lead to uncontrolled virus replication causing YF vaccine-associated viscerotropic disease (YEL-AVD). The illness is similar to wild-type YF and may eventually lead to multiorgan failure and death. YEL-AVD is very rare with a reported number needed to harm (NNH) of 250 000 in US YF vaccinees.[4]

Another SAE is yellow fever vaccine-associated neurotropic disease (YEL-AND) with a NNH of 125 000 in US YF vaccinees.[4] This SAE presents with various clinical neurological symptoms, such as encephalitis and Guillain-Barré syndrome.

On top of immunosuppressive conditions, other factors associated with higher rates of YEL-AVD and YEL-AND include thymus disorders, and age below 6 months or above 60 years.

While booster-vaccination with YF vaccine in 17 persons on tumour necrosis factor α antagonists was performed without SAEs and eliciting a protective immune response in most in a study by Scheinberg *et al*,[8] there is limited data on the outcome of primary YFV in immunosuppressed persons, as it would be unethical to perform an experimental study. A recent case report[9] described immune-protective YF antibodies 2 years after YFV in a 63-year-old woman with Crohn's disease, who had inadvertently received the YFV while receiving adalimumab therapy. Furthermore, a study among a Dutch group of 15 immunocompromised travellers (most of whom received MTX) found protective levels of YF antibodies a median of 33 days after primary YF vaccination.[10] Like our patient, no SAEs were observed in these studies.

In our case report, YF viremia was detected 6 days after the vaccination. This course is similar to that in healthy individuals, where YF viremia is known to occur 3–5 days after inoculation of the YFV.[11] The patient had developed protective antibodies 2 weeks after vaccination, which is also in accordance with the postvaccination course in healthy individuals as YF vaccine provides effective immunity within 10 days for at least 80% of persons vaccinated.[12]

Typically, natural viral infection and live virus vaccination produce a strong and long lasting T-cell-dependent neutralising antibody response,[11] and previous reports have suggested that neutralising antibodies after YF vaccination can be persistently protective for a long period of time in an immunocompetent patient.[13] This has further led to new guidelines on YF vaccination, as the WHO in 2013 concluded that a single dose of YFV is sufficient to confer sustained immunity and lifelong protection against YF disease and that a booster dose of the vaccine is not needed.[14]

Despite immunosuppression, our patient only suffered mild systemic adverse effects following immunisation although some

Table 1 Detection of viremia and neutralising antibodies in relation to time after vaccination

Time after vaccination	*PCR for YF viral RNA	*YF virus-specific IgM titre	*†YF virus-specific IgG titre
2 days	Negative	Negative	Negative
6 days	Positive	Negative	Negative
14 days	Positive	1:80	1:320
6 weeks	Negative	1:20	1:640
3 months	Negative	Negative	1:640
10 months	–	Negative	1:160

*All laboratory tests presented in table 1 were performed at Statens Serum Institut, Copenhagen, Denmark.
†At Centers for Disease Control and Prevention (CDC), a titre of >1:20 is associated with protective immunity after YF vaccination (I B Rabe. Arboviral Diseases Branch, CDC, personal communication, January 2016).
YF, yellow fever.

of her symptoms did resemble initial symptoms of YEL-AVD, and she even developed sufficient antibody response. Owing to a planned holiday in Ghana, further serological testing almost a year after the YFV was performed, confirming that the patient had sustained sufficient, yet decreasing, immunological response to the YFV. In another case,[15] persistent YF seropositivity in an autologous haematopoietic stem cell transplantation recipient has been described. However, in that particular case the vaccine was given before the initiation of immunosuppression, and the immunosuppressive treatment was different from our case.

The variety of immunosuppressive drugs and biological therapies is rising steadily, as are the indications for their use, which contribute to an increasing number of immunosuppressed patients. Our case illustrates that immunisation of immunocompromised individuals possesses various challenges, especially regarding vaccine safety and immunogenicity. These patients are vulnerable to several infections against which vaccines exist, and safe and timely vaccination is therefore of utmost importance. Inactivated vaccines can generally be used without risk, but the patients who are most at risk for infectious morbidity and mortality as a result of their immunosuppressed state are also those least likely to respond to vaccination.

Only persons planning to travel to countries where YF is endemic may need the YFV, and the risk of being infected with YF should always be weighed against the vaccine-associated risk. The risk of being infected is determined by several factors, the most important ones being travel destination and duration, use of mosquito prophylaxis as well as season. The current YF outbreak in Angola and associated mortality serve as an ominous reminder of the importance of vaccination in countries, where YF is endemic.[16]

According to the European Crohn's and Colitis Organisation and Centers for Disease Control and Prevention (CDC),[2–4] live-attenuated vaccines, including YFV, should not be administrated for at least 3–6 months after pausing immunosuppressives, including thiopurins, MTX and biologics. In addition, physicians should keep in mind the immunosuppression induced by long-term corticosteroid treatment. CDC recommends avoiding live-virus vaccination for at least 1 month after stopping high doses systemically adsorbed corticosteroid therapy given for more than 14 days. There are no specific international guidelines concerning when to initiate or restart immunosuppression after the patient has received live-attenuated vaccines, but a period of at least 1 month has been suggested in 'the Pink Book' by CDC.[17]

Learning points

- Yellow fever vaccine and other live-attenuated vaccines are contraindicated in patients currently treated with immunosuppressives, including biologics and until 3–6 months after cessation of these drugs.
- An inadvertently given yellow fever vaccination in a patient with Crohn's disease treated with infliximab and methotrexate was associated with mild systemic adverse effects, and neither yellow fever vaccine-associated viscerotropic disease nor yellow fever vaccine-associated neurotropic disease was observed.
- Despite immunosuppressive therapy, the yellow fever vaccination resulted in protective immunisation after 14 days, identified by a sufficient level of neutralising antibodies that were maintained up to 10 months after the vaccination and possibly longer.

Contributors CE was responsible for writing the case report, apart from the 'background' paragraph and research on background literature. NF-M contributed to all paragraphs, especially the 'discussion', has great knowledge of immunisation of immunosuppressed patients and has been the main contributor of finding background literature. TU wrote the paragraph 'background' and has reviewed the rest of the case report. CA who is a gastroenterologist is in charge of the patient's Crohn's treatment and contributed to all paragraphs of the case report. All authors have contributed to the case report.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 van der Have M, van der Aalst KS, Kaptein AA, *et al*. Determinants of health-related quality of life in Crohn's disease: a systematic review and meta analysis. *J Crohns Colitis* 2014;8:93–106.
2 Rahier JF, Magro F, Abreu C, *et al*. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014;8:443–68.
3 Kroger AT, Sumaya CV, Pickering LK, *et al*. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011;60:1–64.
4 CDC Health information for international travel 2016 (the Yellow Book 2016). http://wwwnc.cdc.gov/travel/yellowbook/2016/advising-travelers-with-specific-needs/immunocompromised-travelers (accessed 27 Feb 2016).
5 Monath TP. Review of the risks and benefits of yellow fever vaccination including some new analyses. *Expert Rev Vaccines* 2012;11:427–48.
6 Staples JE, Gershman M, Fischer M, Centers for Disease Control and Prevention (CDC). Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010;59(RR-07):1–27.
7 Monath T, Cetron MS, Teuwen DE. Yellow fever vaccine. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*. 5th edn. Philadelphia, PA: Saunders Elsevier, 2008;959–1055.
8 Scheinberg M, Guedes-Barbosa LS, Mangueira C, *et al*. Yellow fever revaccination during infliximab therapy. *Arthritis Care Res (Hoboken)* 2010;62:896–8.
9 Nash ER, Brand M, Chalkias S. Yellow Fever Vaccination of a Primary Vaccinee During Adalimumab Therapy. *J Travel Med* 2015;22:279–81.
10 Wieten RW, Jonker EF, Pieren DK, *et al*. Comparison of the PRNT and an immune fluorescence assay in yellow fever vaccinees receiving immunosuppressive medication. *Vaccine* 2016;34:1247–51.
11 Reinhardt B, Jaspert R, Niedrig M, *et al*. Development of viremia and humoral and cellular parameters of immune activation after vaccination with yellow fever virus strain 17D: a model of human flavivirus infection. *J Med Virol* 1998;56:159–67.
12 http://www.who.int/mediacentre/factsheets/fs100/en/ (accessed 1 Dec 2015).
13 Gotuzzo E, Yactayo S, Córdova E. Efficacy and duration of immunity after yellow fever vaccination: systematic review on the need for a booster every 10 years. *Am J Trop Med Hyg* 2013;89:434–44.
14 World Health Organization. *Yellow fever vaccination booster not needed*. Geneva: WHO, 2013. http://www.who.int/mediacentre/news/releases/2013/yellow_fever_20130517/en/ (accessed 1 Dec 2015).
15 Hayakawa K, Takasaki T, Tsunemine H, *et al*. Persistent seropositivity for yellow fever in a previously vaccinated autologous hematopoietic stem cell transplantation recipient. *Int J Infect Dis* 2015;37:9–10.
16 Yellow fever: a global reckoning. *Lancet* 2016;387:1348.
17 Centers for Disease Control and Prevention. *Epidemiology and prevention of vaccine-preventable diseases*. Hamborsky J, Kroger A, Wolfe S, eds. 13th edn. Washington DC Public Health Foundation, 2015;2:20–2.