Author’s response to reviews

Title: A case report of severe recurrent varicella in an ankylosing spondylitis patient treated with adalimumab – a new side effect after 15 years of usage

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Author’s response to reviews:

Dear Editor,

Thank you for the review and careful consideration of our manuscript "A case report of severe recurrent varicella in an ankylosing spondylitis patient treated with adalimumab – a new side effect after 15 years of usage" (INFD-D-18-02003) and the opportunity to revise the paper in order to be acceptable for publication in BMC Infectious Diseases.

We would also like to thank the reviewers for their comments and suggestions for improvement.

Here is our point-by-point response to the reviewers’ comments:

Comments made by Padma Srikanth, MD (Reviewer 1):

The authors have highlighted the occurrence of varicella zoster following immunosuppressive therapy for an autoimmune disorder. The authors are to be commended for documentation of
such a case in a precise manner. The discussion on the use of immunosuppressive therapy and poses a risk for disseminated Varicella zoster.

The following suggestions are made to add more value to the manuscript:

1. Mark the nodular changes in the X-ray & date the X-ray. Is there any calcification around the hilar region on the left. Kindly comment on it.

Authors` response:

Nodular changes were marked with arrows on the X-ray. Figure 2a was taken on the day of admission and Figure 2b after 10 days of therapy, which was also the endpoint of therapy, as explained in the figure legend. According to our radiologist there is no calcification around the hilar region on the left.

Corrections made in the manuscript: Legend of Figure 2.A was corrected into

Figure 2. A. Chest radiograph on the day of admission revealed diffuse nodular infiltrates. B. Radiological resolution of pulmonary infiltrates after 10 days of acyclovir therapy.

2. Was IgM done? What are the values of IgG?

Authors` response:

Before the introduction of adalimumab, serological testing was performed in 2014 and VZV IgG was positive (EIA titre 24) and IgM negative, which indicated past infection with VZV.

During current illness, serological testing for VZV (EIA) performed on the third day of disease, revealed positive IgM (titre 15- ref. pos. >11), positive IgG (titre 36- ref. pos. >11) and positive IgA (titre 12- ref. pos. >11).
The following sentence was corrected in the manuscript “He had had chickenpox at the age of 5, and positive IgG antibodies (titre 24; positive > 11) to varicella-zoster virus (VZV) using EIA in 2014, prior to the initiation of adalimumab treatment”. (Case presentation, page 4, lines 80-82).

The following sentence was also added “Serological testing for VZV using EIA was performed on the third day of illness and IgM (titre 15; positive >11), IgG (titre 36; positive > 11) and IgA (titre 12; positive >11) antibodies to VZV were detected.” (Case presentation, page 4, lines 93-95).

3. What was the target site of the PCR performed for VZV DNA?

Authors` response:

The sample used for VZV PCR was vesicular fluid from the skin, as was mentioned in the original manuscript, line 47 and 92.

4. The authors must explain 'reinfection' and 'reactivation' in VZV for readers to have a better understanding of why VZV occurred in this patient. There are several underlying immunosuppressive conditions such as cancer or post solid organ transplantation states and other immunosuppressants which can pose as risk factors for disseminated VZV. The discussion must include these aspects.

Authors` response:

VZV causes two clinically distinct diseases - primary infection resulting in varicella and herpes zoster resulting from the reactivation of latent VZV that gained access to sensory ganglia during varicella.

Reinfecion/recurrent infection/second varicella infection with VZV is also possible and is more common than is thought [reference 18].
The following text was added/changed: VZV causes two clinically distinct diseases - primary infection resulting in varicella and herpes zoster resulting from the reactivation of latent VZV that gained access to sensory ganglia during varicella [17]. It is traditionally considered that VZV infection provides lifelong immunity but recurrent infection (also referred to as reinfection or second varicella infection) with VZV occur more commonly than previously thought [18, 19]. (Discussion, page 5, lines 114-118)

The following text was also added to the manuscript: Patients with a history of underlying malignancy, steroid use or immunosuppressive therapy, HIV infection, or solid organ transplantation are susceptible for disseminated varicella due to impaired cellular immunity.

Clinical manifestations in the immunosuppressed host can include atypical and severe manifestations such as development of crops of vesicles over weeks, large and haemorrhagic skin lesions, pneumonia, or widespread disease with disseminated intravascular coagulation [17, 21]. (Discussion, pages 5 & 6, lines 122-128)

Also, as two new references were added to the manuscript


the numeration of references was updated throughout the manuscript as well as the reference list.

5. Atypical manifestations of VZV are well described and need to be explained as well, as immunosuppressive therapy can mask the typical presentation of VZV.

Authors` response:

We explained atypical manifestations of VZV in the new added text (lines 122-128), as described in our previous answer.

The following text was also added to the manuscript:
Clinical manifestations in the immunosuppressed host can include atypical and severe manifestations such as development of crops of vesicles over weeks, large and haemorrhagic skin lesions, pneumonia, or widespread disease with disseminated intravascular coagulation [17, 21]. (Discussion, pages 5 & 6, lines 122-128)

6. The manuscript must stress on the early laboratory detection and confirmation of VZV as prompt antiviral therapy leads to better patient outcomes.

Authors` response:

We agree with this comment. It is very important to point out that early diagnosis and treatment are crucial for good clinical outcome.

The following sentence was added at the end of the discussion section:

Early clinical recognition of VZV infection in high risk patients, such are all immunocompromised patients, as well as laboratory detection and confirmation of VZV require early aggressive antiviral treatment leading to favourable clinical outcome [7, 17, 21]. (Discussion, page 6, lines 131-134)

Comments made by Ravi Mahalingam, Ph.D. (Reviewer 2):

Skuhala et al., present a case of a 34-yr-old patient with disseminated skin rash and pneumonitis. They detected VZV-specific Ig G, A and M antibodies in serum and VZV DNA in vesicular fluid. Since the patient has had chickenpox at 5 years of age, the current episode is probably due to reactivation of latent VZV (zoster). The authors need to address this important issue. They repeatedly identify the episode as varicella which is not correct although the overall goal of the study is to show that treatment with adalimumab results in reactivation of latent VZV.
Authors` response:

The aim of this case report was not to point out that immunosuppressive treatment can lead to VZV reactivation (which means herpes zoster- vesicular rash in certain dermatoma, usually without systemic involvement and usually without significant viremia) which is well known fact, but to point out that secondary varicella infection can also occur during immunosuppressive treatment (that means chickenpox- diffuse vesicular rash with systemic symptoms, and during viremia VZV can also reach some other organs such as lungs, brain etc.). Second varicella infection with VZV is also possible and is more common than we thought (reference 18), even in immunocompetent patients.

We did not make any additional changes in the manuscript regarding this comment other than the one already described in our answer to the 1st reviewer.

The following text was added/changed: VZV causes two clinically distinct diseases - primary infection resulting in varicella and herpes zoster resulting from the reactivation of latent VZV that gained access to sensory ganglia during varicella [17]. It is traditionally considered that VZV infection provides lifelong immunity but recurrent infection (also referred to as reinfection or second varicella infection) with VZV occur more commonly than previously thought [18, 19]. (Discussion, page 5, lines 114-118)

Line 78: A VZV-seropositive patient exposed to child with chickenpox may not present with varicella.

Authors` response:

We agree with this statement, but the possibility that reinfection occurs certainly exists. Some of those episodes are well documented, for example in reference no. 19, that was added to the manuscript

Lines 90, 96, 110, 115 and 128: recurrent varicella infection should be changed to zoster.

Authors` response:

We don’t think that “recurrent varicella infection” should be changed to “zoster” because that would be incorrect, since it was second/recurrent varicella (with all clinical features of varicella) following the exposition to person with chickenpox.

We additionally explained the terms varicella, zoster, recurrent varicella/secondary varicella infection/reinfection in our previous answer (Discussion, page 5, lines 114-118).

According to this we did not change the term “recurrent varicella” to “zoster”.

Figure 2: nodule infiltration should be identified using arrows.

Authors` response:

Nodular infiltrations were marked with arrows and added on the X-ray Figure 2.

Attached please find our revised manuscript with all described corrections listed above. Each of the co-authors has reviewed and approved the revisions made.

We hope that you will find this revised version of our manuscript suitable for publication in your journal.

With kindest regards,

On behalf of all co-authors:

Tomislava Skuhala, MD, PhD