Standard antifungal therapy for pulmonary cryptococcosis to improve prognosis

Masaya Taniwaki and colleagues[1] report an interesting case of pulmonary cryptococcosis mimicking lung cancer. The patient was confirmed to have pulmonary cryptococcosis through both bronchoscopic examination and CT-guided biopsy. After antifungal treatment for several days, the mass in the lungs had not decreased in size and the patient refused to continue therapy, continuing only with observation. After a discussion about the antifungal therapy given and a review of the literature, we concluded that the effect of therapy might have been more obvious if standard treatment had been given.

The clinical practice guidelines for cryptococcal disease, updated in 2010 by the Infectious Diseases Society of America,[2] are the most authoritative source on crypotoccal disease. According to the guidelines, once a diagnosis of cryptococcal disease has been confirmed, the clinician should establish whether or not the patient is in a state of immunosuppression, which is not mentioned in the Clinical Picture. If the patient is not immunosuppressed, they should receive oral fluconazole therapy (400 mg per day) for 6–12 months, whereas if the patient is immunosuppressed, a more complex therapy should be given. However, in this case, the patient received oral fluconazole 200 mg daily for 9 days, which is a lower dose and shorter course than recommended. If the patient had received a more standard therapy of fluconazole initially, in terms of dose and course, the effect might have been more obvious and he might have decided to continue treatment.

It is difficult to observe remission of pulmonary cryptococcosis on imaging in only a few weeks. We suggest that the authors contact the patient to persuade him to continue antifungal treatment for at least 6 months, until the mass shadow improves, instead of observation only, to guarantee the treatment effect.

We declare no competing interests.

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Authors' reply

We thank Boyou Zhang and colleagues for their interest in and comments on our Clinical Picture.[1] To the best of our knowledge, our patient was not immunosuppressed because none of the following causes of immunosuppression were present: HIV infection, human T-cell leukaemia virus type 1 infection, immunosuppressive drugs, malignant diseases, diabetes, splenectomy, renal disease, or liver disease.

We treated the patient for cryptococcosis according to the Japanese national guidelines.[2] We first administered oral fluconazole 200 mg daily for 9 days, but this did not lead to improvement on chest radiography. Because we considered his infection to be severe, we then administered oral voriconazole 600 mg daily for 1 day, and then 400 mg daily for 3 days.

It has been reported that cryptococcal infection can lead to granuloma formation.[3] It has also been reported that cryptococcosis can cause organising pneumonia.[4] In the present case, granuloma formation and organising pneumonia might have been present when mass enlargement was observed on CT scan. In cryptococcal disease, fluconazole resistance has been reported.[5] The patient might have had fluconazole-resistant cryptococcal infection. Cryptococcosis with granuloma and organising pneumonia might gradually improve only after treatment with several antifungal agents.

We declare no competing interests.

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VIVIANE study of HPV vaccination

Since the 2018 Cochrane meta-analysis on human papillomavirus (HPV) vaccination[1] quotes the VIVIANE publication,[2] we found it interesting to analyse some results of this study on the most relevant clinical endpoints—namely, cervical intraepithelial neoplasia grade 2 or

greater (CIN2+) and grade 3 or greater (CIN3+) and adenocarcinoma in situ. To date, the VIVIANE trial is the study with the longest duration of follow-up (up to 7 years). Despite the participants being older than 25 years, in the according-to-protocol cohort for efficacy, 56·5% of participants in the vaccinated group and 56·5% of participants in the control group were DNA-negative and seronegative for both HPV 16 and 18. In the total vaccinated cohort, 57·3% of participants included in the vaccinated group and 54·0% of participants included in the control group were DNA-negative and seronegative for both HPV 16 and 18. We are therefore surprised that the authors do not provide specific information and analyses that might be relevant to these patients.

Since the vaccine did not show any effect on the rate of all CIN2+ irrespective of HPV type (table 4 in the Article[2]), the vaccine's effect among women who were DNA-negative and seronegative for HPV 16/18 would be interesting to know. Even post-hoc and subject to certain limitations, this analysis would have had the merit of providing valuable insight into the effectiveness that might be expected from HPV routine vaccination in girls. Indeed, these results might represent the best approximation available to date of HPV routine vaccine efficacy in uninfected women because the vaccine is ineffective in women already infected and therefore not therapeutic.[3]

Similarly, the authors mention that there were 50 CIN3+ cases (including four women with adenocarcinoma in situ) in the group of vaccinated women and 45 CIN3+ (one woman with adenocarcinoma in situ) in the unvaccinated group. To our knowledge, we are the first to point out these results, which is surprising given their clinical relevance: CIN3+ and adenocarcinoma in situ are the precancerous lesions that are least likely to regress spontaneously.[4,5]

This result has not been analysed statistically, but the relative risk for CIN3+ can be calculated as 1·11 (95% CI 0·75–1·66) and for adenocarcinoma in situ as 4·00 (0·45–35·79). These data do not show any efficacy for the vaccine in preventing high-grade cervical lesions. These results have not been commented on by the authors, but their relevance is obvious.

For the sake of transparency, the authors should present, analyse, and comment on all the data. Beyond this single publication, the existence of these results raises the question of the validity of the method and conclusions of Cochrane meta-analysis,[1] where they have not been considered.

CR co-founded Re-Check, a non-profit organisation specialised in investigating and mapping health affairs. CR and J-PS are co-authors of an investigative book on the HPV vaccination ("La piqûre de trop?", Xenia, 2010) and published four investigations in Swiss mainstream media on HPV vaccine. CR and J-PS co-authored a comment on Cochrane HPV vaccine MA's methodology and a Letter to Editor on this topic in *British Medical Journal* and *EBioMedicine*. RB and CM-T declare no competing interests.

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Authors' reply

Although we agree that cervical intraepithelial neoplasia grade 2 or greater (CIN2+) and grade 3 or greater (CIN3+) are essential clinical endpoints in vaccine efficacy studies for HPV, we disagree with Rémy Boussageon and colleagues on several points.

The authors claim that we do not provide specific information and analyses that might be relevant to patients. In line with good publication practice, we focused our Article[1] on the reporting of the results of the prespecified primary and secondary endpoints of the trial, which reflect what the trial was designed for. The comment that it would have been interesting to know the vaccine's effect among women who were DNA-negative and seronegative for HPV 16/18 is puzzling and suggests little understanding of the analysis cohorts. As outlined in the methods, the appendix, and the discussion, the according-to-protocol cohort for efficacy was the primary analysis cohort for efficacy. Endpoints related to HPV 16/18 were evaluated in women who were DNA-negative and seronegative for the corresponding HPV type at month 0 and DNA-negative at month 6. We strongly disagree with the suggestion that this DNA negative and seronegative subset of women aged 26–72 years would represent the effectiveness expected from HPV routine vaccination in adolescent girls. Besides HPV DNA and serostatus, the biology and epidemiology of HPV infection are very different in adult women versus the adolescent target population. The proportion of women in our trial who had received previous treatment for HPV 16/18 at baseline is typical for this age group in the general population.