Letter to the Editor

The presence of anti–SARS-CoV-2 antibodies does not necessarily reflect efficient neutralization

We read with interest the article by Gargouria et al. (Gargouria et al., 2022), which described the cases of 4 patients with recurrent SARS-CoV-2 infection despite "the presence of (anti–SARS-CoV-2 S1 IgG) antibodies." Although the continuous emergence of new and highly mutated SARS-CoV-2 variants is posing paramount challenges to adaptative immunity (Lippi et al., 2021), the message delivered by the authors is not supported by data and is thus potentially misleading.

The analysis of data published by Gargouria et al. (Gargouria et al., 2022) reveals first that anti–SARS-CoV-2 S1 IgG antibodies were measured with a commercial immunoassay displaying a suboptimal negative predictive value for neutralizing antibodies (i.e., 71% vs 80-95% of other IgG immunoassays) (Montesinos et al., 2021). It is hence likely that several samples of patients with low values of these antibodies may retain significant neutralizing potential. The second aspect concerns the anti-S1 IgG antibodies values in the patients. In one of the cases (case #4), serological assessment was performed 1 week after receiving a positive result for molecular testing, as admitted by Gargouria and colleagues (Gargouria et al., 2022) and thus no reliable indications can be garnered on anti-S1 IgG antibodies titer immediately before the second infection. In addition, for cases #2 and #3, the samples were collected between 12 and 14 days before recurrent infection, with anti-S1 IgG antibodies levels appearing only 2.49-fold to 3.75-fold higher than the method-specific cutoff, while it is clear that efficient viral neutralization could only be achieved with higher values. To this end, Bubonja-Šonje et al. reported that >80% neutralizing activity of anti-S1 IgG antibodies (measured with the same test) could only be reached with values around 10, achieving up to 100% neutralization when anti-S1 IgG antibodies values were >20 (Bubonja-Šonje et al., 2021). Therefore, although we would formally agree that "reinfection occurred despite the presence of antibodies" (Gargouria et al., 2022), the authors should have instead concluded that "reinfection occurred with the presence of low values of anti-S1 IgG antibodies" in both these cases. The same concept applies to case #1, which was the only where serological testing could be performed on the same day of the reinfection episode because the anti-S1 IgG antibodies level was 3.46, thus around the same threshold associated with just 60% viral neutralization (Bubonja-Šonje et al., 2021).

In conclusion, caution should be exercised in interpreting results of anti–SARS-CoV-2 antibodies testing, wherein the presence of anti–SARS-CoV-2 antibodies does not necessarily reflect efficient neutralization.

Conflict of Interest

None.

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