Diagnostic stumbling blocks in the COVID-19 monitoring of medical staff while putting hygiene requirements into practice

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During the initial phase of the coronavirus disease 2019 (COVID-19) global pandemic, we began performing close monitoring of employees who returned from vacation from high-risk areas or who had symptoms that were associated with COVID-19. This strategy was implemented to avoid nosocomial transmission and infection chains within hospital staff. In this context, we identified a 36-year-old colleague (patient A) who reported experiencing a 1-day loss of sense of smell. The day after, he was tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by PCR (RNA extraction with QIAamp Viral RNA kit; Altona SARS-CoV-2 PCR). The amplification curve was below the assay thresholds but clearly above the negative controls, which, in concert with clinical observations, was interpreted as the beginning of measurable SARS-CoV-2 replication, leading to an immediate 14-day quarantine in order to avoid nosocomial transmission. During this time, he developed a mild transient cough, a feeling of burning chest and 4 days of malaise before fully recovering before the end of the quarantine. Immediately after quarantine, serum specimens were sampled weekly and tested with four line probe antibody assays (Fig. 1) and the BioRad Platelia SARS-CoV-2 IgA/IgM/IgG enzyme-linked immunosorbent assay (ELISA), with negative results up to week 6 after onset of symptoms, except a weak but reproducible IgM band in the Vazyme assay (Fig. 1(A)).

Patient B was the partner of a colleague who returned from a skiing vacation in a neighbouring community of the Austrian epicentre. He was tested and found to be positive by PCR (ct E-Gene: 31.25 (positive control (PC): 30.58), ct S-Gene: 30.69 (PC: 29.87), ct Internal Control (IC): 28.78 (PC: 28.77)) and had 10 days' febrile but nonhospitalized flulike disease with a serious cough. IgM and IgG testing was negative 4 weeks after the positive PCR result, and was only weakly positive for IgG antibodies 9 weeks after the positive PCR result (Fig. 1(B)). ELISA testing revealed a positive result 1.5-fold higher than the PC.

Patient C, a 29-year-old colleague, also tested positive by PCR (ct E-Gene: 29.98 (PC: 27.69), S-Gene: 29.22 (PC: 26.66), IC: 25.54 (PC: 25.66)) and developed a minor IgG response visible in four assays (Fig. 1(B)), although the patient was completely asymptomatic during the entire observation period. Surprisingly, the corresponding ELISA result was 3.9-fold higher than the PC, indicating a strong IgA response that could not be measured with the four rapid antibody assays.

Although for patient A no follow-up PCR tests were possible as a result of local quarantine restrictions, the case is of major importance because it demonstrates that a PCR result in the early phase of infection could falsely be interpreted as negative and thus may lead to subsequent nosocomial infection of patients and/or colleagues. Furthermore, a relatively mild clinical course of COVID-19 may be associated with a lack of, or at best marginal, antibody response, thus leading to the conclusions that an immunity passport, as discussed in several European countries, including Germany, is not reliable and reasonable, and that antibody screenings ought not be the method of choice for monitoring healthcare workers in order to avoid nosocomial transmissions.

Patient A displayed a weak positive serologic response that was only detected because five different in vitro diagnostics (IVD)s were used; otherwise, the case would likely have been classified as negative had a different diagnostic scheme been applied.

In concert with the recent study by Long et al. [1], who reported that antibody response in asymptomatic patients is weak and disappears rapidly, it cannot be concluded that a negative antibody assay indicates that person being tested is not infected with SARS-CoV-2 and thus is protected against reinfection or incapable to infect others, especially as the hot topic of antibody protection remains under consideration. Hygiene concepts based on close monitoring of medical staff therefore cannot be based on routine interpretation of laboratory diagnostics but instead require a more personalized diagnostic approach, with a special focus on borderline cases that do not

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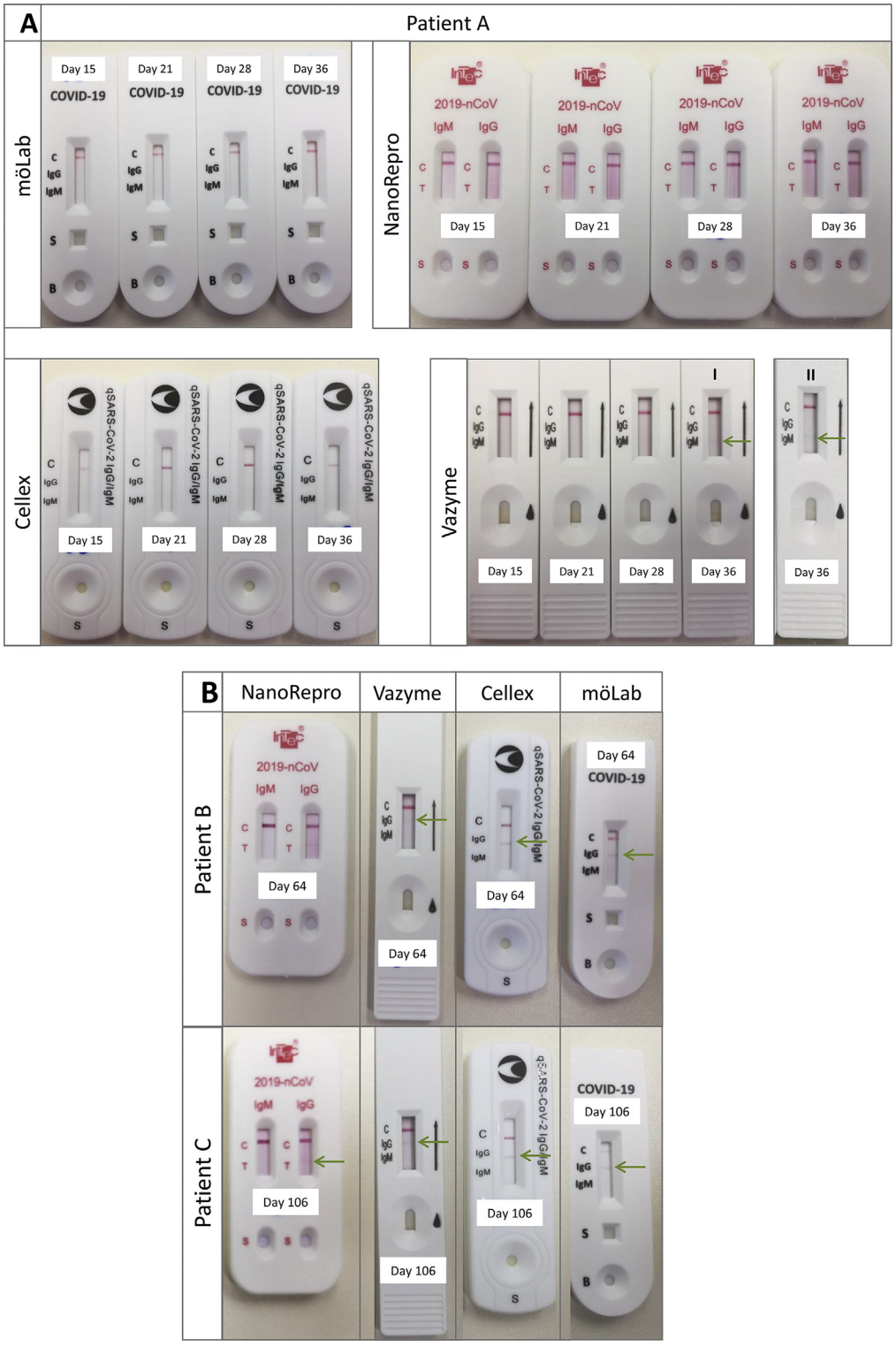

FIG. 1. Detection of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies with line probe assays offered by möLab, Cellex, Vazyme and NanoRepro. Despite symptoms, patient A shows only weak IgM signal in Vazyme test 5 weeks after weak PCR signal (A). Patients B and C show only weak IgG signals 9 and 15 weeks after SARS-CoV-2 PCR, although these results were clearly positive (B).

obviously fulfil the criteria for positivity. In the above-described cases, infection chains were interrupted even in the case of shared households.

Conflict of interest

None declared.

Reference

[1] Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 2020.