3. Maisch B, Alter P. Treatment options in myocarditis and inflammatory cardiomyopathy : Focus on i. v. immunoglobulins. Behandlungsoptionen bei Myokarditis und inflammatorischer Kardiomyopathie: Immunglobuline i. v. im Fokus. Herz. 2018;43(5):423–30.
4. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433.
5. Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: Possible mechanisms. Life Sci. 2020;253:117723.

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Strengths and weaknesses of the diagnostic tests for SARS-CoV-2 infection☆

Virtudes y dificultades en los test diagnósticos de la infección por el SARS-CoV-2

To the Editor:

SARS-CoV-2 is an RNA virus belonging to the coronavirus family that causes COVID-19. Since the description in china of the first cases until our current pandemic, this disease has presented major clinical challenges for health systems in every country. From a clinical point of view, it can manifest itself in various ways: from asymptomatic, through bilateral pneumonia, and on to adult respiratory distress syndromes.[1] To date, the diagnosis has been based primarily on tests that confirm the presence of SARS-CoV-2, since the symptoms that patients present can be common to other viruses, bacteria or even some atypical bacteria. We must not forget to evaluate these symptoms so as to rule them out as possible causative agents of the disease we observe. Up to now, when it is suspected that SARS-CoV-2 is the cause of the infection, the *gold standard* determination is *real-time reverse-transcription polymerase chain reaction* [RT-PCR]).[2] However, despite the usual high sensitivity and specificity of the RT-PCR tests, on several occasions clinicians have encountered patients with high clinical suspicion (epidemiological, clinical, analytical, and radiological criteria) and with repeatedly negative PCR results. For this reason, first of all we wonder whether the location from where the specimen is obtained is ideal. The test is performed with nasopharyngeal exudate because that is the region where the virus experiences a higher rate of replication. However, other alternative specimens could also be used, such as oropharyngeal exudate, sputum, saliva or bronchoalveolar lavage (the latter implies a greater risk for the personnel who obtain the specimen). Secondly, we question whether the specimen is collected and transported to the laboratory in a suitable manner and without contamination and, thirdly, if the specimen has been optimally processed to obtain the maximum performance of the test.

Given that RT-PCR is a test that requires at least 4–6 hours to complete and its costs are high, recent efforts in the diagnosis of COVID-19 have also focused on *enzyme-linked immunosorbent assays* [ELISA]), and on rapid antigen and antibody tests (Table 1). On the one hand, the ELISA test is an immunoenzymatic test that determines the presence of IgM and IgG antibodies, or a combination of IgM + IgA. The cost of this test is low, and it takes about 3.5–4 hours. On the other hand, the rapid test is a lateral flow chromatographic immunoassay, and it enables results to be obtained easily in 20–60 min, but with low sensitivity.

Table 1
Comparison of the principal diagnostic tests against COVID-19.

	RT-PCR	ELISA test	Rapid antibody test
Type of specimen	Nasopharyngeal or oropharyngeal swab	Serum or plasma	Serum or plasma
Objective	Detection of SARS-CoV-2 virus RNA by exponential amplification of complementary DNA detected in real time	Detection of IgM/IgG or IgG RBD (viral protein receptor-binding domain) antibodies by a colorimetric assay	Detection of IgM/IgG antibodies by colour change of the strip in the lateral flow assay
Advantage	*Gold-standard* diagnostic test: detects the presence of the virus directly with more precise results at disease onset	Low price, robust detection of seroconversion status, can detect IgM/IgG accurately several days after infection onset	Very low price, easy to use (use at both the point of care and at home), fast results (20–60 minutes) and accurate detection of IgM/IgG several days after infection onset
Limitations	It is a laborious and expensive test, which requires numerous reagents and specialised equipment It can lose sensitivity after five days from symptoms onset, and it is susceptible to specimen collection errors Runtime 4–6 hours	Low sensitivity in the first days of illness. Requires rigorous cross-reactivity testing with another immune response and needs to be performed in the laboratory with specialised equipment Runtime 3.5–4 hours	Low sensitivity in the first days of illness. Requires rigorous cross-reactivity testing

It should be noted that the rapid antibody tests and the ELISA tests provide additional information on the patient's immune status compared to the RT-PCR test[3] (Table 1), although it is still unknown if they can indicate a patient's immunity to future reinfections. The weak points of these techniques are low sensitivity (close to 50%) in the first 7 days of the disease (increasing as days go by to 88%), and the results being affected by the patient's immune status.[4] For these reasons, the information provided by these tests is of little use in many cases and of no use at all in some cases, such as in patients with some types of immunodeficiencies. However, the advantages of the rapid tests include the speed in which they provide the results, simplicity of use and price.[2] In addition, the confirmation of suspected cases of COVID-19 through serolog-

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ical tests could help reduce the risk of exposure to patients, as well as avoid carrying out a RT-PCR and thus reserve its use for other patients.[5]

Therefore, despite the fact that the current diagnostic tests for a new virus have some deficiencies, the performance is steadily improving, and possible errors in how and from where the specimens are obtained are being corrected, converting them into a foundation to help the clinician make diagnostic-therapeutic decisions.

References

1. Wang D, Hu B, Ch Hu, Zhu F, Liu X, Zhang J, et al. Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9, http://dx.doi.org/10.1001/jama.2020.1585.
2. Castro R, Luz PM, Wakimoto MD, Veloso VG, Grinsztejn B, Perazzo H. COVID-19: a meta-analysis of diagnostic test accuracy of commercial assays registered in Brazil. Braz J Infect Dis. 2020, http://dx.doi.org/10.1016/j.bjid.2020.04.003.
3. Marson, A., Hsu, P., Bern, C., Whitman, J., Hiatt, J., et al. COVID-19 Testing Project. Recuperado 8 de mayo de 2020, de https://covidtestingproject.org/about.html.
4. Padoan Andrea, Cosma Chiara, Sciacovelli Laura, Faggian Diego, Plebani Mario. Analytical performances of a chemiluminescence immunoassay for SARS-CoV-2 IgM/IgG and antibody kinetics. Clin Chem Lab Med. 2020, http://dx.doi.org/10.1515/cclm-2020-0443.
5. Long Q, Liu B, Deng H, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med. 2020, http://dx.doi.org/10.1038/s41591-020-0897-1.

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Diffuse large B cell lymphoma associated with methotrexate in a patient with acute lymphoblastic leukemia☆

Linfoma difuso de células grandes B asociado a metotrexato en un paciente afecto de una leucemia linfoblástica aguda

Dear Editor,

Lymphoproliferative disorders (LPD) associated with iatrogenic immunodeficiency and related to methotrexate are exceptional outside the context of patients with autoimmune diseases,[1] however, some studies suggest that its incidence is somewhat higher in the last decade.[1] Although the aetiology is not well defined, methotrexate (MTX) is an immunosuppressant that inhibits nucleic acid synthesis and this could cause an increase in the number of Epstein-Barr (EBV) viral DNA copies, the latter having a well-known implication in the development of LPD.[2,3] MTX-associated LPDs form a morphological spectrum similar to post-transplant LPDs. There is no consensus regarding treatment, but it is of general opinion that the strategy of suspending MTX-treatment and repeating the imaging tests between 4 and 8 weeks later is the first option before starting chemotherapy treatment.[2,4]

We present the case of a 52-year-old man, allergic to metamizole, ex-smoker, with a pathological history of gastroesophageal reflux, colonic diverticulosis, and intraductal papillary mucinous neoplasm of the pancreas that required a cephalic pancreatectomy in 2013. Due to presenting severe asthenia in August 2016, a diagnosis was made of acute lymphoblastic leukaemia (ALL) negative BCR-ABL study and MLL rearrangement. Induction chemotherapy treatment was started following the 2011 high-risk PETHEMA group protocol (prednisone, vincristine, daunorubicin, L-asparaginase, and intrathecal therapy), achieving a complete remission with negative minimal residual disease (MRD). Three + 3 consolidation cycles were given based on MTX (cumulative dose of 12 g/m^2), cytarabine and L-asparaginase, maintaining a good elimination of MRD at all times. Maintenance treatment was started in February 2017 with intramuscular MTX 38.2 mg per week and oral mercaptopurine 100 mg, which was maintained until May 2018 with a cumulative total MTX dose of 25,212 mg. In May 2018, the patient presented a fever and odynophagia. The physical examination revealed a tumour of about 4 cm in the soft palate with left lateral displacement of the uvula. A nasal endoscopy was performed that showed a nasopharyngeal lesion with no apparent bulging or abscess. A positron emission tomography/computed tomography (PET/CT) scan was performed, which showed metabolic uptake in the tumour lesion with a hypometabolic center of necrosis affecting the nasopharynx, as well as level II and III bilateral hypermetabolic lymphadenopathies. A nasopharyngeal biopsy was performed, which showed areas of extensive necrosis with viable tissue replaced by sheets of large atypical cells with frequent mitosis. Immunohistochemistry showed atypical cells, positive for CD20, PAX5, focal BCL-6, MUM1, EBER and with a 90% Ki-67 proliferation index. The histological diagnosis was LPD associated with iatrogenic immunodeficiency, and the differential diagnosis weighed between a mucocutaneous ulcer and a diffuse large cell lymphoma (DLCL). The histology and the extension to the regional lymph nodes tipped the scales in favour of a DLCL.

Once all the results were available, the diagnosis was an EBV-positive B-cell lymphoproliferative disorder compatible with a iatrogenic immunodeficiency-associated DLCL.

Treatment with MTX was suspended and the imaging test (PET/CT) was repeated at 4 weeks, which showed complete metabolic remission and which is maintained in the last update at 12 months of follow-up.

The fact that the patient has a history of ALL for which he was receiving treatment with MTX, with a moderate cumulative dose for a relatively short period of time (14 months) and with complete remission which was still maintained at 12 months of drug suspension, without the need to start chemotherapy, highlights our case as unique. This entity in a patient with ALL has not previously been published and this may help with its future characterisation.

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