cal data and complementary tests. Treatment is guided mainly by symptoms, although glucocorticoids are a mainstay. It has recently been reported that adding rituximab to the regimen helps reduce disease recurrence.[7]

Therefore, in spite of the low prevalence of pleural involvement in IgG4-related disease,[13] given the good response to treatment with corticosteroids, it is advisable to rule out this entity in patients with predominantly lymphocytic exudative pleural effusion of unknown cause, even in the absence of other suggestive systemic manifestations. Multidisciplinary management of these cases is essential.[14]

Conflict of interests

The authors declare that they have no direct or indirect conflict of interests related with the contents of this manuscript.

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Chylothorax secondary to dasatinib☆

Quilotórax espontáneo secundario a dasatinib

Dasatinib is a potent second-generation BCR-ABL1 tyrosine kinase inhibitor (TKI) that is used at a daily dose of 100 mg as first-line therapy in patients with maintenance-stage chronic myeloid leukemia (CML), and in patients resistant or intolerant to previous therapy.[1,2]

Dasatinib has been associated with the development of pleural effusion (PE), produced by different mechanisms.[3] Secondary chylothorax has rarely been described in the literature.[4–9]

Clinical case

Our patient was a 63-year-old woman who attended the emergency department with a 2-month history of dyspnea on exertion and in left lateral decubitus, without fever, chest pain, or constitutional symptoms. She had a previous diagnosis of CML, and had been receiving oral dasatinib 100 mg/day for a year. On examination, her breathing was normal and her general status was good; BP: 146/80 mmHg; temperature: 35.5 °C; heart rate: 80 beats/min; SpO_2: 97%. Pulmonary auscultation identified decreased breath sounds in the lower left field, with signs of PE. All other parameters were normal. The chest X-ray revealed PE in the left lower third field, with a normal cardiac silhouette (Fig. 1A).

Blood count showed 5900 leukocytes with 54% neutrophils, 25.4% lymphocytes, 7.2% eosinophils, hemoglobin 12.8 g/dl, mean corpuscular volume 90.6, platelets 24,2000, ESR 34 mm. Biochemistry, autoimmune tests and immunoglobulins were normal. Thoracentesis yielded milky-looking pleural fluid (PF), with the following values: glucose 90 mg/dl, albumin 2.30 g/dl, LDH 152 u/l, proteins 5.05 g/dl, cholesterol 106 mg/dl, triglycerides 334 mg/dl, CEA 1.2 ng/ml, rheumatoid factor < 10 IU/ml, ANA negative, leucocytes 1470/mm^3, RBCs 3000/mm^3, mononuclear cells 98.8%, polynuclear cells 1.2%. Cytology showed predominantly lymphoid reactive cytoarchitecture with some elements of myeloid ontogeny and no evidence of malignancy. Bacterial culture includ-

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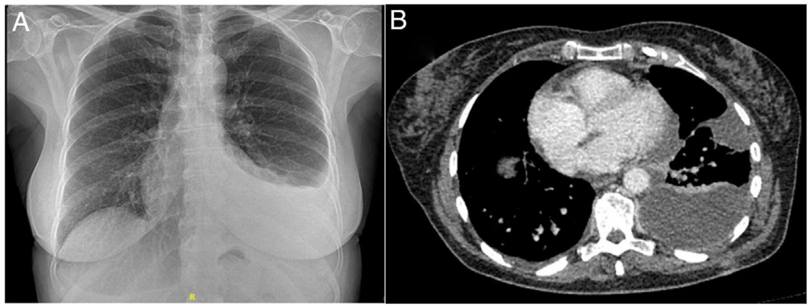

Fig. 1. A) Chest X-ray showing left pleural effusion. B) Computed axial tomography (mediastinal window) showing free and organizing left pleural effusion.

ing Lowenstein was negative. Pleural biopsy revealed mesothelial hyperplasia. The echocardiogram was normal.

Dasatinib was discontinued and a chest drain was inserted, yielding 1,600 ml after 5 days of admission, and a visit was scheduled for 15 days later. Chest computed tomography (CT) 10 days after discharge showed left organizing PE (Fig. 1B). A new thoracentesis showed amber-colored PF, pH 7.55, glucose 148 mg/dl, LDH 169 u/l, cholesterol 120 mg/dl, triglycerides 81 mg/dl, proteins 5.32 g/dl, leukocytes 2874/mm^3, polynuclear 31.8%, mononuclear 68.2%, red blood cells 5000/mm^3; 600 ml fluid was evacuated. The patient's progress was favorable following administration of 60 mg prednisone for 15 days in a tapering regimen, and switching dasatinib to imatinib. PE resolved with no sequelae observed on chest CT a month later.

Discussion

Although edemas and hydrosaline retention have been associated with TKIs used to treat CML, exudative PE[3] and even chylothorax have frequently been reported with dasatinib.[4–9] Immune mechanisms have been implicated in its production, due to the presence of predominantly lymphocytic exudate. Alternatively, it has been proposed that PE (transudate or exudate) might also be caused by blocked T cell function at clinically relevant concentrations, affecting proliferation, activation and cytokine production, or inhibition of platelet-derived growth factor receptor ® (PDGFR-®) expressed in pericytes involved in angio-lymphangiogenesis.[10] Other authors suggest that PDGF-BB and its receptor, PDGFR-®, are directly lymphangiogenic.[11]

The first cases of dasatinib-associated PE were described by Bergeron et al. in 2007 in a series of 40 patients, of which 9 developed respiratory symptoms, with PE in 7 cases, lymphocytic exudate in 6, some accompanied by predominantly lymphocytic alveolar infiltrates.[12]

Risk factors include age and advanced disease, cardiac and autoimmune disorders, preexisting hypertension, hypercholesterolemia, skin rash, dose and time of administration, and lymphocytosis.[3–8] Correlations with minimum plasma levels, drug exposure, duration and response to treatment have also been suggested but not confirmed.

The frequency, risk factors, and outcomes associated with PE were assessed in a pooled population of 11 trials that included 2712 patients with CML and acute lymphoblastic leukemia treated with dasatinib. PE developed in 6%–15% of at-risk patients annually. With a minimum follow-up of 5–7 years, drug-related PE occurred at a rate of 28 %–33%. In multivariate analysis, age was the main risk factor. Despite PE, the overall response to dasatinib, progression-free survival, and survival were similar in patients who developed PE and in those who did not.[3]

In an experimental study in rats treated with dasatinib for 5 weeks, PE appeared with rapid and reversible increase in the paracellular permeability of monolayers of pulmonary endothelial cells, resulting in increased passage of macromolecules, loss of endothelial cadherin (primary cell adhesion molecule), rupture of cell bonds, and development of actin stress fibers. These results were replicated in human umbilical and venous endothelial cells, confirming a decrease in endothelial resistance. This increase in endothelial permeability is a mechanism dependent on reactive oxygen species (ROS) *in vitro* and *in vivo*.[13]

Chylothorax is defined as a turbid PE with triglycerides > 110 mg/dl and cholesterol levels < 200 mg/dl, which gives it its characteristic color.[14] Chylothorax is associated with multiple etiologies, but dasatinib is the only drug known to be associated with this adverse effect. Chylothorax has been reported in 14 cases, including our patient.[4,15] Our case is the first in the literature to show the biochemical change from chylothorax to lymphocytic PE as an expression of improved permeability before resolution, after discontinuing treatment.

Although treatment discontinuation will resolve symptoms, given the therapeutic benefit of dasatinib, dose reduction rather than complete discontinuation has been proposed, although this still needs to be demonstrated. Dasatinib may be temporarily suspended until chest drainage and supportive measures achieve symptomatic improvement, and resumed at reduced dose, although steroids, pleurodesis, and even thoracic duct ligation have also been recommended as in our case.

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Statistical and mathematical modeling in the coronavirus epidemic: some considerations to minimize biases in the results☆

Modelado estadístico y matemático en la epidemia del coronavirus: algunas consideraciones para minimizar los sesgos en los resultados

To the Editor

The new coronavirus (SARS-CoV-2)[1,2] has demonstrated the heavy health and socioeconomic impact that an epidemic can have worldwide. In the face of such pandemics, governments and health authorities must act quickly[3] and implement policies that aim to limit the transmission of the virus, avoid the collapse of the health system, and reduce the morbidity and mortality associated with the virus - strategies all driven by the need to prioritize resources in settings where they are scarce. In this respect, supporting decision-making with the use of mathematical models can be a key factor. These tools are potentially useful for explaining and predicting the speed and manner in which the virus spreads, in order to support health planning, identify and stratify patient risk, and establish prognosis from electronic records.

A crucial consideration in the area of mathematical modeling is that the data collected are usually observational in nature. This may lead to significant bias in the results obtained from the systematic application of conventional statistical techniques.[4] Another important factor is incomplete information,[5] such as censored and lost data. As no diagnostic tests are performed in many cases, it is impossible to know whether or not they are infected. In addition, endpoints such as recovery or death have not yet been reached during the course of the study. Moreover, patients with no symptoms or mild symptoms are the least likely to visit a doctor or even have a diagnostic test. Again, ignoring the effects of missing or censored data may confer significant bias on the conclusions reached.[5]

From a statistical point of view, the study design may be more important than the amount of data collected. However, in a health emergency, governments may be overwhelmed and data may be collected from severe cases only. To determine the actual extent of the pandemic, random population sampling is necessary. A clear exception to this SARS-CoV-2 crisis is the case of South Korea and Singapore, where population tests were conducted systematically, allowing outbreaks of infection to be isolated more quickly, to the extent that the effects of the virus were mitigated more quickly than in other countries.

From an epidemiological point of view, it is important to highlight the need to identify variables that indicate patient risk and prognosis. The most popular indicator is undoubtedly the mortality risk, which measures the likelihood that a patient will die if he or she has the disease. Precise estimations are not simple, and as indicated above, given the observational nature of the recorded data, the presence of biases is customary. According to Lipsitch et al.,[6] biases occur because of a delay in recording information or because there is a preponderance of patients at higher risk in the database. A potential solution to this problem in the analyses is to stratify patients into different groups based on their severity and prognosis. The use of specific techniques to manage causal inference or missing data, such as the Propensity Score or doubly robust estimators, is also recommended.[7] This approach can improve statistical inference drawn from patients belonging to each stratum.

The large discrepancies in the proportion of symptomatic patients and the mortality risk associated with SARS-CoV-2 underline the need to adopt these approaches. On March 5, 2020, the percentage of asymptomatic patients reported by the European Center for Disease Prevention and Control was 80%. However, in a study of patients from the Diamond Princess cruise ship, this figure was 20%.[9] In the latter case, the study sample comprised a greater proportion of older patients with a higher probability of presenting symptoms, making it difficult to extrapolate the conclusions to the general population. Similarly, the fatality rate varies significantly (estimates range between 0.4% and 15%[10]), partially due to the problems mentioned. The precise characterization of these variables based on the epidemiological profiles of the population is essential to understand the transmission mechanisms of the virus[11] and predict future care demands.

A basic criticism of epidemic modelling is that parameters are frequently adjusted according to government-provided statistics on infected subjects, despite the fact that very few countries can provide clear evidence that these figures reflect the real situation, given the lack of knowledge about the percentage of asymptomatic patients and lack of overall testing among the population. In fact, asymptomatic patients may be the main transmitters of the virus.[11]

Mathematical models can be an important tool for anticipating future developments and supporting decision-making. However, if data are inaccurate and specific techniques to correct the observational nature of the recorded data are not used, conclusions may be biased. In this regard, all relevant institutions should make an effort and openly provide high-quality data,[12] so that scientists can

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