C) BRIEF CASE REPORTS

Infective endocarditis secondary to an infrequent agent in a patient with haemodialysis

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Dear Editor,

Concerning the case recently published in this journal,[1] we report the case of a patient with haemodialysis who experienced septic shock owing to endocarditis, caused by *Klebsiella oxytoca* and *Staphylococcus aureus*.

Klebsiella spp is an atypical agent of infective endocarditis, reaching < 1.2% in primary valves and 4.1% in prosthetic valves.[2] The most frequent aetiological agent is *K. pneumoniae*, which has only been found in 4 published cases of infection caused by *K.* oxytoca.[3]

We report the case of a 58-year-old male patient with stage V chronic kidney disease owing to lupus nephritis treated with haemodialysis through a permanent right jugular catheter. His previous medical history showed chronic ischaemic heart disease, hypertension and receiving treatment of corticosteroids. Having no previous symptoms, he ran a temperature of > 39º C and felt a general discomfort. The examination revealed signs of hypotension, tachycardia, grade III/VI heart murmur (heard everywhere else in the body) and temperature. The blood test findings were as follows: leukocytes: 25,900 (N: 90%, L: 4%, M: 6%), Hb: 9mg/dl, anisopoikilocytosis with spherocytes and macrocytes, hypersegmented neutrophils, positive direct Coombs's test and normal liver and pancreatic profiles. The abdominal ultrasound and the thorax X-ray did not show any interesting pathological data. These, in addition to a negative urine culture, ruled out any sources of infection in those areas. *S. aureus* and *K. oxytoca* were isolated in the blood cultures of the catheter and the peripheral blood cells. This is why a transthoracic echocardiogram was carried out, leading to the discovery of a 2.5 x 1.5cm wart in the posterior medullary velum of the mitral valve and a smaller-sized one in the anterior medullary velum of the tricuspid valve. Following these findings, a treatment of vancomycin and gentamycin was administered according to an antibiogram, which later revealed a spleen embolism and a cardiogenic shock, resulting to the patient's death.

K. oxytoca represents 0.5-0.6% of all isolations in bacterias; more than a third of those are polymicrobial infections and between 37 and 52% are nosocomial.The majority are caused by the biliopancreatic or urinary pathology, and the various types of infective endocarditis are extremely rare, with a very high mortality rate (49%) despite receiving adequate antibiotic treatment.[4,5]

Given the immunosuppression of our patients following a substitute treatment, its associated comorbidity and the risk of contracting nosocomial infections, a quick detection of infective endocarditis is necessary since an early antibiotic treatment reduces the high risk of morbidity and mortality.

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Acute renal failure associated with Pemetrexed (Alimta®)

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Dear Editor,

Pemetrexed disodium (Alimta®, Eli Lilly) is a chemotherapy agent belonging to the antifolates class and it is approved for the treatment of patients with mesothelioma and non-small cell lung cancer. It is almost exclusively excreted by kidneys and, although very sporadic, some acute renal failure cases have been reported associated with its use, such as the one described as follows:

A 56-year-old male patient with a medical history of smoking 40 cigarettes per day, and having worked in coal mines for 16 years. He met the criteria for chronic bronchitis and suffered from osteoarthritis. In March 2008 he was diagnosed with stage IV adenocarcinoma of the lung (bilateral pulmonary nodules), following the accidental discovery of a pulmonary mass in a chest X-ray. He received treatment with carboplatin and taxol between April and September 2008, with good tolerance and mid-term response to CT scan. The patient's check-ups showed no complications until December 2008, when the progression of the pulmonary lesions was discovered. This is why a treatment of Pemetrexed was administered at a dose of 500mg/m^2(953mg) by means of IV every 3 weeks, together with folic acid and Vitamin

B_{12} supplements. The patient received the first five cycles with no complications. The serum creatinine in the first cycle was 0.76mg/dl, similar to the following two; in the fourth it was 1.1mg/dl and in the fifth 1.6mg/dl (glomerular filtration rate estimated with MDRD-IDMS at 44.9ml/min/1.73m).[2] Pemetrexed was not administered in the sixth cycle due to severe anaemia (24% haematocrit) with no signs of haemorrhage and with normal leukocytes and platelets, as well as non-oliguric acute renal failure with a serum creatinine of 5.2mg/dl. The patient was hospitalised in order to be tested and treated. A month and a half beforehand, he had received IV contrast to perform a CT scan. During re-examination, the patient also mentioned that for several months he was taking three daily doses of 600 milligrams of ibuprofen as a treatment for osteoarthritis pain. An abdominal ultrasound revealed the presence of a possible hepatic metastasis of 2.1cm in the left hepatic lobe; the kidneys and the prostate were of normal size and there was no hydronephrosis. The 24-hour protein excretion in the urine was 112mg. A conservative medical treatment was chosen with blood transfusion, parenteral hydratation and diuretics. The patient had an adequate diuresis at all times without signs of hydroelectrolitic imbalance. This is why there were no plans for a haemodialysis. There was a gradual yet slow recovery of the renal function. The patient was discharged after 2 weeks to continue with oncology tests. Two months later, the serum creatinine was 3.3mg/dl without any further complications.

The technical record of the medicine shows that in clinical studies patients with a creatinine clearance of ≥ 45ml/min do not require dose adjustments different from those recommended for all patients. There are no sufficient data on the use of Pemetrexed in patients with creatinine clearance.[1] In our patient, the analysis coinciding with the fifth cycle of Pemetrexed was truly within this limit. The technical record also underscores that the concomitant use of non-steroidal anti-inflammatory drugs should be avoided. In our case it went undetected and they could have contributed to the appearance of acute renal failure. The IV contrast administered 2 weeks after the fifth cycle could have also contributed to the initial deterioration of the renal function. Nonetheless, the chronological sequence of the clinical data makes us consider Pemetrexed as the main cause. This medicine is excreted in an unaltered way almost exclusively through the urine (70-90%). It does not undergo metabolism and it can be found in 81% of the plasma proteins. Its plasma clearance decreases in the presence of an altered glomerular filtration rate. In patients with normal renal function, its half-life is 3 hours,[2] and there are reports of its accumulation in ascitic fluid.[3] There are reports of all types of renal failure in 2.4% of the patients during phase III clinical tests.[2] In cases previously published, the reason for renal failure was attributed to a toxic acute tubular necrosis, although no kidney biopsies have been reported in any of the patients. Some patients fully recover,[4,5] while others need chronic dialysis.[3] Also in one case, there were reports of the induction of nephrogenic diabetes insipidus together with renal tubular acidosis through three treatment cycles.[4] Concerning therapeutic management, it is not clear which method is the most effective to reduce the toxic levels of the drug in the context of an overdose or a renal failure. Continuous venovenous dialysis does not appear to reduce large amounts of the drug, and it is unknown if other types of dialysis can improve its clearance. There are positive preliminary reports on the use of thymidine[5] and of leucovorin[3] as antidotes. Another agent with possible beneficial effects is carboxypeptidase G2; however, it is necessary to gain more clinical experience on this agent, as well as on thymidine and leucovorin.[3]

In short, we report a new case of acute renal failure associated with Pemetrexed. It is necessary to emphasise the need to scrupulously respect this drug's technical specifications, as well as those of other chemotherapy agents which also have a wide therapeutic range, to minimise the risk of possible side effects. Another challenge is the treatment of cancer patients with organic dysfunctions, such as renal failure, with a dose of chemotherapy drugs that are as safe as those administered to patients without such dysfunctions.[6]

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