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Gabapentin and hypersensitivity syndrome

Sir,

A 35-year-old lady presented with a one-week history of high fever with rigors, headache, lower back pain and nausea. The patient had a past history of a benign breast lump and glandular fever as a teenager. She had been taking 300 mg of gabapentin daily for two months for a trapped nerve in the left groin following a fall from a horse but was otherwise well. Examination revealed abdominal flank tenderness and a temperature of 40°C. Urinalysis showed blood and protein. Her blood results showed a low total white cell count of 1.5 x 10^9/l specifically with lymphocytopenia and neutropenia. Her liver function tests revealed a total protein of 82 g/L and ALT of 55 U/L (Range 0-40 U/L), but were otherwise normal. A provisional diagnosis of pyelonephritis was made. The patient was commenced on gentamicin and piperacillin with tazobactam intravenously due to her neutropenia.

Despite treatment her temperature remained persistently raised between 38 and 41°C with rigors. After seven days she developed tender bilateral cervical lymphadenopathy. There were no other palpable lymph nodes. Multiple urine cultures and several blood cultures yielded no growth or pyuria. A viral cause for her illness was considered. All viral serology, including Epstein Barr virus (EBV) IgM, toxoplasma, cytomegalovirus, parvovirus B19, hepatitis A, B and C, and HIV, were negative. The EBV IgG was positive indicating previous glandular fever infection, which was known. Autoantibody serology was also negative. Chest and abdomen radiographs were normal, as was an abdominal and renal tract ultrasound examination. A contrast CT scan of her abdomen and thorax was also normal; in particular, there were no abnormal lymph nodes or collections seen.

The fever and leucopenia persisted for 10 days despite intravenous antibiotics. At this point the gabapentin was discontinued, as a known adverse effect of gabapentin is leucopenia. Over the following two days the patient’s fever and symptoms resolved. The patient remained afebrile, her full blood count had returned to normal ranges and her lymphadenopathy resolved. The virology screen was repeated and was again negative. She was discharged home one week later.

Hypersensitivity syndrome (HSS) is a rare condition that can occur with any drug. Diagnosis is clinically based, with variable symptoms appearing anywhere between one week to three months after the introduction of the implicated drug.\(^{[1]}\) It was first described in relation to antiepileptic agents in 1950\(^{[2]}\) and is reported to effect 0.01-0.1% of patients taking antiepileptic medication.\(^{[3]}\) The mortality is estimated at 10%, but may be higher in those with liver involvement. Signs and symptoms include rash, fever, tender lymphadenopathy, hepatitis, eosinophilia and other hematological abnormalities and facial oedema.\(^{[1]}\) The duration of HSS is dependent on the continuation of the offending treatment. Symptoms resolve promptly on discontinuation of the implicated medication.\(^{[3]}\) Whilst a rash is present in about 90% cases, it was not detected in the case discussed. The mechanism of hypersensitivity syndrome relating to gabapentin is, to date, unknown.

Gabapentin has been used successfully as an alternative in patients with hypersensitivity to older antiepileptics\(^{[3]}\) and is considered to be a relatively safe drug with a more favorable side-effect profile than older medication.\(^{[1-3,5]}\) There is one previous case report of gabapentin-induced hypersensitivity syndrome;\(^{[6]}\) this was reported in a 72-year-old gentleman who developed confusion, fever, diffuse macular rash and splenomegaly nine
days after gabapentin was introduced. The signs and symptoms resolved rapidly after discontinuing the medication. Alternative diagnoses were considered. A virus was originally suspected, yet the patient tested negative for all viruses reported to cause leukopenia, cervical lymphadenopathy and very high fever. The patient was initially treated for suspected pyelonephritis. In retrospect this is unlikely in view of multiple negative blood and urine cultures, the presence of cervical lymphadenopathy and the lack of response to treatment. It is the opinion of the authors that an interaction between the antibiotics and gabapentin was unlikely. There are no previously documented interactions between gabapentin and either gentamicin or piperacillin with tazobactam. There are cases of the antibiotics above (especially piperacillin) causing hypersensitivity reactions, but in this case the hypersensitivity symptoms pre-date the antibiotic administration. Naranjo’s algorithm, a systematic method of objectively determining the probability of adverse drug reaction having occurred, was applied to this case. A score of 6 was calculated, equating to a “probable” adverse reaction to gabapentin.

The Committee on Safety of Medicines, based in the United Kingdom, report 1186 adverse reactions to gabapentin, of which only one relates to hyperpyrexia and one to pancytopenia.

In summary this was a case of a young person with self-limiting high fever, leukopenia and bilateral cervical lymphadenopathy. In this case, any possible infective cause for her combination of symptoms was excluded. It was concluded the illness was directly caused by the gabapentin medication.

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