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FATAL AGRANULOCYTOSIS DEVELOPED IN THE COURSE OF CARBAMAZEPINE THERAPY*

A Case Report and Review of the Literature

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A case of fatal agranulocytosis in an adolescent who was on carbamazepine therapy is presented. The clinical and laboratory findings suggest that the primary cause of the disorder was neutropenia rather than infection, and the preceding factor for neutropenia was carbamazepine. The timing of occurrence of the hematologic picture, its dependency on dose increments, and the lack of symptoms until infection supervened are consistent with an idiosyncratic-toxic drug reaction (type 2 drug reaction). This is the first reported agranulocytosis case due to crabamazepine in adolescence.

As carbamazepine is a commonly used, major anticonvulsant, physicians should be aware of its side effects, such as agranulocytosis[1]. We have not encountered any report in the literature of agranulocytosis due to carbamazepine during childhood or adolescence. We present a case of fatal agranulocytosis with skin rash and a former reaction against phenytoin in the adolescent period.

Case Report

S.Z., a 14-year-old boy, underwent surgery with the diagnosis of "triventricular hydrocephaly" due to a right temporal arachnoid cyst in the third ventricle one month earlier. His leukocyte count was 8600/mm^3 at that time. Phenytoin (6 mg/kg) administration was initiated post-operatively for prophylactic purposes and carbamazepine (8 mg/kg) was added the next day, after the patient's first convulsion. He developed a high fever on the tenth day of treatment, which subsided after discontinuation of phenytoin.

The carbamazepine dose was increased to 12 mg/kg on the fifteenth day of admission when the patient's leukocyte count was found to be 4800/mm^3. He was discharged on the twentieth day of therapy in good general health. One

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day later he was admitted to the Pediatrics Service with complaints of fever and skin rash which covered his trunk and extremities. He had not ingested any drug except carbamazepine for fifteen days.

The patient's vital signs included a body temperature of 38.5 °C, pulse 112/min, respiratory rate 32/min, blood pressure 110/80 mmHg. The trunk and limbs were covered with a erythematous maculopapular rash. The neurological examination revealed brisk deep tendon reflexes, bilateral Babinski response, patellar clonus and bilateral optic atrophy as in his previous examination one month before.

Laboratory findings were as follows: hemoglobin 14 g/dl, hematocrit 44%, leukocyte count 2000/mm^3. All of the 23 leukocytes which could be detected on the blood smear were lymphocytes. thrombocytes were abundant, and erythrocytes were normochromic and normocytic. Urine analysis, liver and kidney function tests and chest x-ray were normal. Computerized cranial tomography showed triventricular hydrocephaly. A ventricular tap showed normal cerebrospinal fluid values. The recurrent bacterial cultures of blood, urine, throat, stool and cerebrospinal fluid were negative. Antinuclear antibody, anti-DNA, C3 and C4 were normal. The specimen of bone marrow aspiration was acellular.

Mezlocillin, amikacin and hydroxyzine administration was initated with the diagnosis of neutropenic sepsis and allergic reaction. Carbamazepine was discontinued. The patient had severe gastroenteritis between the third and eighth days of admission. On the fourth day, the leukocyte count fell to 1400/mm^3, and all of the 10 leukocytes which could be detected on the blood smear were lymphocytes. The leukocyte count began to increase and the fever resolved on the fifth day. On the blood smear, relative lymphocytosis and relative monocytosis preceded the development of early granulocyte precursors, band forms and polymorphonuclear leukocytes. On the sixth day, mezlocilline was discontinued and vancomycin, piperacillin, ornidasole and fluconazole were added as the patient's condition deteriorated. On the seventh hospital day, the patient developed adult respiratory distress syndrome (ARDS), symptoms of which supervened to symptoms of severe gastroenteritis and then intrinsic renal failure. Peritoneal dialysis and assisted ventilation were initiated. He died on the twenty-second day, just after developing disseminated intravascular coagulation as a complication of ARDS and pneumothorax. Post-mortem blood culture revealed Klebsiella.

Discussion

The patient displayed an acquired single cytopenia as neutropenia, the other series being unaffected. The etiology of acquired neutropenia is suggested to be drugs and toxins, preleukemia, systemic diseases and infections, and idiopaty[2]. Drugs and/or infection seem to be the most likely causes of our patient's

neutropenia. It cannot be distinguished precisely whether primarily an infection caused the neutropenia or whether infection supervened a primary neutropenia. The most common viral infections associated with leukopenia are infectious hepatitis, infectious mononucleosis, rubella, measles and occasionally influenza[3]. None of these infections seem to be the primary cause of our patient's neutropenia, fever and skin rash, which were noted one day after his discharge and one day before his readmission to the hospital. During his stay in the hospital he had no symptoms attributable to any infection up to the date of discharge. It would seem unlikely that the causative agent of his initial fever associated with skin rash was bacteria as we had failed to grow bacteria in the consecutive blood cultures. We believe that gastroenteritis developed due to mucosal damage caused by serious bacterial invasion of the bowel wall by the microorganisms of the flora because of the limited granulocytic response[4], leading to sepsis which gave rise to ARDS, Thus we searched for other possible causative factors, such as a medication, carbamazepine was the only medication the patient had been ingesting.

The most common hematologic side effect of carbamazepine was reported to be thrombocytopenia followed by aplastic anemia, agranulocytosis, pancytopenia and bone marrow suppression. The incidence of agranulocytosis due to carbamazepine was found to be 0,71/506,000[1]. Although cases of agranulocytosis due to carbamazepine have been reported in adults, we did not encounter any case in the literature regarding children or adolescents.

Leukopenia due to carbamazepine which may be persistent or transient is compatible with a toxic or idiosyncratic drug reaction (type 2 reaction)[5-7] because of its development after dose increments and liability to emerge in patients with low or low-normal leukocyte counts, its initiation during the first and second weeks of treatment and its asymptomatic nature unless an infection supervenes[1,5,6]. As expected in a type 2 reaction, leukopenia due to carbamazepine rarely turns to agranulocytosis or aplastic anemia[1]. However, it has been pointed out that no case of leukopenia due to carbamazepine precede marrow suppression[8]. Essentially, the cases in the literature involve severe leukopenia and agranulocytosis which have arisen abruptly within one month of therapy without following a definite period of leukopenia. Our case is consistent with those in the literature from the viewpoint of the starting time. Besides, the development of agranulocytosis symptoms six days after the dose increment and the association with fever reinforces the resemblance to a type 2 agranulocytosis reaction.

Our knowledge about the bone marrow morphology in cases of carbamazepine-induced agranulocytosis is quite limited[6,9,10]. In our patient we could not obtain material on bone marrow aspiration during the neutropenic period and could

not repeat it because of the patient's deteriorated condition. Nevertheless, the rapid rise in the leukocyte count after the cessation of the drug, the emergence of the early myelocyte precursors which preceded the stab forms and neutrophils, and the transient monocytosis during the first two days indicated that recovery of hypoplastic or aplastic bone marrow which is usually observed in type 2 agranulocytosis cases had begun[5].

Another interesting point in our case was the presence of a reaction against both phenytoin and carbamazepine. There are many reported cases in which at least one or more findings such as skin rash, blood dyscrasias, fever, and deterioration of liver function tests are found during sequential phenytoin and carbamazepine therapies[6,11]. The reactions of our patient against both phenytoin and carbamazepine probably resulted from his increased production and/or decreased detoxification of the common arene oxide metabolites[11]. His ingestion of the two drugs together for ten days is expected to have raised the level of these toxic metabolites and may have deteriorated the reaction. This points out that carmazepine and phenytoin should not be used together or sequentially, if any adverse effect is encountered with one of them.

The third interesting point in the case is the presence of agranulocytosis with skin rash, which may arise in various forms[1,12]. Skin rash has been declared as an indication for the cessation of the drug[6]. A patient who elicited simultaneous skin rash and agranulocytosis on the twenty-first day of carbamazepine therapy, as in our patient, was previously reported[13]. On the other hand, it has been proposed that rash would not be seen in leukopenic patients[14].

Although some authors advise hematologic monitoring[15,16]. It is not generally recommended because it will detect only reversible leukopenia of which the incidence is 10-12%, but not fatal and rapidly developing leukopenia[1,8]. Our patient's leukocyte count on the seventeenth day (4800/mm^3) was found to be normal, but severe leukopenia and agranulocytosis were discovered five days later.

If we could have investigated the effect of carbamazepine on the granuloid precursors (C colony assay) of the patient after his recovery and shown a decrease in CFU-C colony numbers when carbamazepine was added in the culture, we could have proved that the causative agent was carbamazepine; however, the deteoriated condition of the patient made this investigation impossible. On the other hand, absence of any other medicine besides carbamazepine on admission and absence of any report of agranulocytosis after cessation of phenytoin strongly suggests that agranulocytosis was caused by carbamazepine.

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