AGRANULOCYTOSIS DURING CLOZAPINE THERAPY

Sir,

Agranulocytosis, defined as granulocyte count less than 500-cells/mm^3, is a serious complication of clozapine therapy. It occurs frequently in the first three months and 95% cases occur within the first six months of treatment (Young et al.,1998). Its one-year cumulative incidence is 0.8% (Alvir et al.,1993). This complication has no relation with clozapine dose and presently, it is difficult to predict who will develop it (Honigfeld et al.,1998). In contrast to the Western literature, only one case of clozapine-induced agranulocytosis has been

reported in the Indian counterpart (Srinivasan & Thomas,1998). We report another case of agranulocytosis.

A 26 years old man, introvert premorbidly, was admitted with the ICD-10 (World Health Organization,1992) diagnosis of undifferentiated schizophrenia of seven years. One of his second-degree relative had an unspecified mental illness. Following hospitalization, clozapine was started in view of poor prior response to conventional antipsychotics. It was gradually increased to 600 mg/day. Baseline blood studies were within normal limits except raised total WBC counts (12,400-cells/mm^3). Medical history and examination failed to reveal any disorder that might have presented with leukocytosis. Consequent to EEG showing 16 episodes of generalized spike, polyspike and wave complexes lasting 200-1200 m.sec in a 30 minutes record, sodium valproate was started at 12th week and titrated to 800 mg/day. Patients' hematological profile was done regularly revealing the following results. With few fluctuations, his eosinophils count steadily increased from 7% (623 cells/mm^3) at second week after starting clozapine to a maximum of 40% (6360 cells/mm^3) at 16th week. No allergies or any eosinophilia related disorder were found on examination or in history, however, he was empirically given two doses of albendazole (400 mg) at 14th and 15th weeks. Meanwhile, total WBC count fluctuated between 6,200 and 11,900 cells/mm^3 up to 13th week, from when it increased to its maximum (15,900 cells/mm^3) at 16th week. Soon afterward, it suddenly dropped to 8,500 cells/mm^3 (neutrophils: 52%, 4240 cells/mm^3) at 17th week and to 1,300 cells/mm^3 (neutrophils: 18%, 234 cells/mm^3) at 18th week. Concurrently he developed pyrexia (39°C) and all the drugs were immediately discontinued. Following an urgent physician consultation, along with reverse isolation, broad-spectrum antibiotics were started. Since there were practical difficulties in acquiring granulocyte-colony-stimulating factor (G-CSF), lithium 300 mg/day, in view of its WBC count increasing property, was started. He gradually improved and the total WBC count, on the fourth day of conservative management, was 4,500-cells/mm^3 (neutrophils count of 630-cells/mm^3).

This patient was on clozapine and sodium valproate at the onset of WBC decline. An association between sodium valproate and neutropenia was reported earlier (Symon & Russel,1983); however, its association with agranulocytosis is unknown. Presently, sodium valproate is considered as the agent of first choice in the management of clozapine-induced seizures (Young et al.,1998). Due to these reasons, we considered clozapine but not sodium valproate as the causative agent for agranulocytosis.

Our patient had no known risk factors of agranulocytosis such as female sex, increased age and age less than 21 years (Alvir et al., 1993; Alvir & Liberman, 1994). A notable finding in this patient was persisting eosinophilia that peaked just before the onset of WBC decline. This is an interesting phenomenon given the fact that an association has been noted between clozapine-induced eosinophilia and neutropenia (Galletly et al.,1996; Lucht & Rietchel, 1998). Since eosinophilia has higher incidence rate (Hummer et al., 1994) and all patients with eosinophilia do not develop either neutropenia or agranulocytosis, we could not explain the significance of eosinophilia. There are possibilities of influence of some intervening factors, hence, we suggest that other factors that might precipitate agranulocytosis, in the presence of eosinophilia, should be investigated.

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