Lithium Carbonate Failed to Modify the Neutropenia Associated with Large Granular Lymphocyte Proliferation

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Large granular lymphocyte (LGL) proliferation is a rare lymphoproliferative disorder characterized by absolute or relative lymphocytosis with bone marrow infiltration and neutropenia [1]. The expanded lymphocytes are often medium-sized cells with abundant cytoplasm containing many azurophilic granules. Different membrane phenotypes have been reported, though most cases display a suppressor/cytotoxic phenotype [2]. The disease usually follows a chronic, relatively indolent clinical course; however, the associated neutropenia can be responsible for recurrent and sometimes fatal infections which often represent the only clinical sign of the disease. The mechanism behind this neutropenia is not clear but the evidence that normal LGLs can inhibit bone marrow macro-phage-granulocyte colony-forming units (GM-CFU) in vitro may provide a pathogenic link. In fact, some patients with LGL proliferations show a reduction of GM-CFUs in bone marrow [1].

The therapy of LGL proliferations remains controversial for the majority of patients. At present chemotherapy is generally only given to patients with progressive disease; those few achieving a response have not shown increased survival. Since infectious complications remain the major cause of morbidity and mortality in these patients, it is possible that measures which correct neutropenia might result in clinical benefit and prolonged survival.

The concept of bone marrow restoration by means of pharmacological stimulation is not a new one and successful recovery of hematological parameters has been reported in patients with hairy cell leukemia,

using lithium carbonate [3]. Moreover, administration of lithium has improved neutropenia in cases of Felty's syndrome, aplastic anemia and neutropenia following cancer chemotherapy [4]. It has been shown that lithium carbonate can increase granulocyte production in psychiatric patients and normal subjects exerting sequential effects on myelopoiesis by increasing the production of colony stimulating factor from monocytes/macrophages and by enhancing the effects of colony stimulating factor on the growth of GM-CFU [5].

The following is the first report on the use of lithium carbonate in neutropenia associated with LGL proliferation. We have treated 3 patients with severe neutropenia ($< 0.5 \times 10^9/l$) causing recurrent infections. Two had a CD3 + , CD8 + , CD16+, HNK-1 + phenotype and showed a clonally rearranged T β locus, whereas the 3rd one was CD3-, CD8-, CD11 + , CD16+, CD2+

with TB locus in germline configuration. All of them suffered from frequent upper respiratory tract infections, one had a septicemia due to *Staphylococcus epidermidis* and another one complained of chronic pharyngitis. Thus, they were quite often on antibiotic treatment. Lithium carbonate was administered orally for 3 months and the dosage was adjusted to maintain a serum lithium level between 0.6 and 1.0 mEq/l determined weekly or biweekly. The mean daily dosage of lithium was 835, 1,450, 1,200 mg with average serum lithium levels of 0.35 ± 0.1 , 0.8 ± 0.03 , 0.7 ± 0.07 mEq/l, respectively. No untoward side effects of the lithium therapy have been observed except for gastric intolerance to higher

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dosages in the 1st case. The absolute neutrophil count was evaluated every 7–15 days and remained stable below $0.5 \times 10^9/l$ throughout lithium treatment in all cases. In agreement with the persistence of neutropenia the patients did not show any clinical improvement while on therapy.

There are two possible explanations for ineffectiveness of lithium carbonate in this clinical trial. Possibly the lithium levels in the patients were too low. It is accepted that serum levels above 0.55 mEq/l produce an optimal increase in neutrophil counts [4]. In the 1st case we certainly did not reach the optimal dose of lithium for inducing granulocytosis because of gastric intolerance. Alternatively, there could be considerable variation among neutropenias in their sensitivity to lithium, but we have to accept as true failures the 2 cases with higher levels of the drug. Our results suggest that lithium is unable to correct this particular neutropenia. The study of additional patients will allow to confirm this observation.

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