

Hypereosinophilia Caused by Calcium Folinate

A Case Report

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Hypereosinophilia may be associated with various clinical disorders, e.g. parasitic, bacterial or mycotic infections, pulmonary, haematological, gastrointestinal, immunological or rheumatic diseases, and cancer.^[1,2] However, it is most often associated with adverse drug reactions.^[1,2]

We describe a case of hypereosinophilia after the use of antianaemic drugs, and an analysis of the case seems to implicate calcium folinate.

Case Report

In March 1985, a 72-year-old woman was admitted to our hospital with microcytic anaemia (RBC $3.75 \times 10^{12}/L$, haemoglobin 82 g/L, haematocrit 0.27 as a fraction of 1.00, mean cell volume 70fL). Her history included arthritis due to rheumatic fever at the age of 17 years, a right nephrectomy for lithiasis at the age of 50 years, and hysterectomy at the age of 57 years.

Clinical and laboratory examinations indicated that the anaemic condition was due to chronic bleeding secondary to both acute erosive duodenitis and oesophagitis, and a hiatal oesophageal hernia.

Specific treatment was initiated with ferrous gluconate 125 mg/day intravenously, intramuscular cyanocobalamin [vitamin B12] 5000 µg/day and intramuscular calcium folinate 1.5 mg/day, resulting in normalisation of the red cell parameters. In December 1985 and January 1987, the woman

was again admitted with anaemia and was treated with the same protocol with ready improvement. On both occasions, no change in the leucocyte pattern was found.

In April 1991, the woman was admitted for an episode of melaena. Endoscopy showed the presence of bloody erosions of the gastric antral mucosa. The blood chemistry panel showed a hyposideraemic microcytic anaemia (RBC $3.08 \times 10^{12}/L$, haemoglobin 71 g/L, haematocrit 0.22 as a fraction of 1.00, mean cell volume 73.3µL, iron 2.32 µmol/L), with a normal leucocyte pattern [WBC $4200 \times 10^6/L$, eosinophils 0.05 as a fraction of 1.00 ($195 \times 10^6/L$)]. Again, therapy was initiated with ferrous gluconate 125 mg/day intravenously (Ferlixit-Rhône-Poulenc Rorer SpA, Milan, Italy, product by Natterman & Cie GmbH, Colonia, Germany), intramuscular cyanocobalamin 5000 µg/day (Dobetin-ACR Francesco Angelini ACRAF SpA, Rome) and intramuscular calcium folinate 1.5 mg/day (Lederfolin, Cyanamid Italy SpA, Catania, Italy).

Over the following days, a progressive increase in eosinophils was noted (fig. 1): 11 days after the onset of therapy, the eosinophils were 0.21 as a fraction of 1.00 ($1247 \times 10^6/L$) peaking after 14 days at 0.37 as a fraction of 1.00 ($2352 \times 10^6/L$). On that day, antianaemic therapy was discontinued. The hypereosinophilia was completely asymptomatic. After the discontinuation of therapy, both the absolute number and percentage of eosinophils

gradually diminished, returning to a value of 0.07 as a fraction of 1.00 ($319 \times 10^6/\text{L}$) in a control performed 54 days later. In the meantime, all clinical and laboratory investigations excluded the presence of parasitic, neoplastic, immunological and/or rheumatological disease.

From May to October 1991 the patient underwent treatment with ferrous gluconate only, with no increase in the percentage or absolute number of eosinophils. At the end of November 1991, she began monotherapy with intramuscular calcium folinate 1.5 mg/day in an attempt at a challenge test, with a gradual slow increase in eosinophils, which peaked at 0.17 as a fraction of 1.00 ($4210 \times 10^6/\text{L}$) after 19 days, at which time calcium folinate therapy was discontinued. Subsequently, the eosinophils decreased progressively to a value of 0.07 as a fraction of 1.00 in about 30 days. In January 1992, the patient received only intramuscular

cyanocobalamin 5000 µg/day for approximately 4 weeks without any change in absolute number and percentage of eosinophils.

At the end of July 1993, after a blood chemistry panel check again showed hypochromic anaemia, the woman's general practitioner prescribed therapy with intramuscular calcium folinate 1.5mg twice a week, intramuscular cyanocobalamin 5000µg twice a week and ferrous gluconate 125 mg/day intravenously. Once again, the woman presented a rapid increase in eosinophil number, with a maximum of 0.23 as a fraction of 1.00 ($3670 \times 10^6/\text{L}$) after 35 days, at which time calcium folinate and cyanocobalamin were discontinued. Thereafter, eosinophils progressively decreased to a value of 0.06 as a fraction of 1.00.

In February 1994, the woman died from an acute myocardial infarction. The autopsy excluded

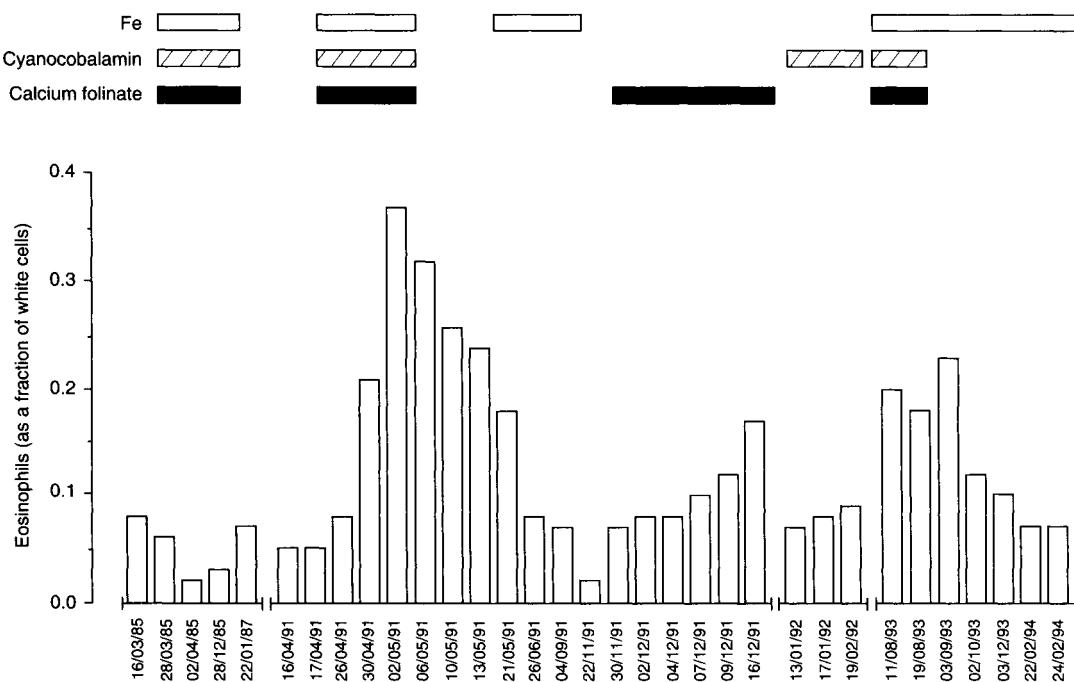


Fig. 1. The correlation between the assumption of ferrous gluconate (Fe), cyanocobalamin (vitamin B12) and calcium folinate therapy and the number of eosinophils expressed as a fraction of 1.00.

the presence of neoplastic, immunological and infectious diseases.

Discussion

The incidence of calcium folinate-induced adverse effects is very low. In fact, in spite of the extensive use of this substance in therapy, only a few cases of adverse effects have been reported; these include central nervous system effects (altered sleep patterns, irritability, excitability, seizures), psychotic reactions, gastrointestinal system effects (nausea, abdominal distension, flatulence), dermatological effects (urticaria, erythema, pruritus) and allergic reactions.

In the present case, the development of hypereosinophilia was probably related to the combined use of antianaemic drugs as it occurred twice (April 1991 and August-September 1993), with a similar time course. However, the use of ferrous gluconate alone for 4 months (May-October 1991), as well as the use of cyanocobalamin alone for 4 weeks (January 1992) did not cause any change in the total number of eosinophils. On the other hand, the use of calcium folinate alone (December 1991) induced a gradual increase in eosinophils. The adverse phenomenon seems to be immunomediated, considering that during previous hospital admissions in 1985 and 1987, the patient received ferrous gluconate, cyanocobalamin and calcium folinate without any variation in the leucocyte pattern. The hypereosinophilia appeared only during a subsequent exposure to these drugs for antianaemic treatment in 1991. This seems to exclude an idiosyncratic nature, and supports the hypothesis of an adverse effect due to an immunological mechanism.

The causes of an abnormal increase in eosinophils after the combined use of calcium folinate and cyanocobalamin cannot be explained from the

available data. Nevertheless, we can only speculate that the complex kinetic^[3] and dynamic^[4] interrelationships between cyanocobalamin, calcium folinate and/or their metabolites may play a role in the immunomediated process; in particular, since interleukin-5 is a well known growth factor for eosinophils,^[5] an association between calcium folinate and this cytokine can be envisaged.

No similar cases are described in the literature. Rare cases of anaphylaxis are reported for anti-anaemic drugs: one with folic acid,^[6] and some after intramuscular injection of cyanocobalamin.^[7,8] More recently, an IgE-mediated reaction to intramuscular injection of hydroxycobalamin was reported in a patient who had pernicious anaemia.^[9]

Thus, the use of antianaemic drugs, in particular calcium folinate, should be included among the iatrogenic causes of hypereosinophilia.

References

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