worthy of mention are the possible interactions between catechins and drugs that could be administered to cancer patients for the treatment of concomitant diseases. In fact, it has been shown that EGCG, by inhibiting both CYP3A4 and P-glicoprotein activities, increased the bioavailability of the calcium channel blockers verapamil and diltiazem,[8,9] thus raising the risk for patients to undergo atrioventricular block. The inhibition of CYP3A4 activity by green tea extracts could increase the plasma concentrations of midazolam[4] and, therefore, amplify the risk of prolonged sedation. On the contrary, the up-regulation of CYP1A2 could result in reduced bioavailability of the antipsychotic drug clozapine.[6] Furthermore, both green and black tea extracts inhibited the activity of the isoforms 1A1 and 1A3 of sulfotransferases,[10,11] a family of enzymes involved in the metabolism of drugs such as methyldopa or β2-adrenoceptor agonists, thus increasing their plasma concentrations and side effects. With regard to the plasma concentrations of EGCG in people drinking green tea, it is interesting to note that the values found by Chow and colleagues and quoted by Shah et al[2] could be underestimated. In fact, Chow et al measured plasma EGCG after a single administration of green tea to healthy volunteers. Considering that catechins are metabolized by sulfotransferases and the latter is inhibited by the former,[10,11] catechin plasma concentration could significantly increase in people consuming a large amount of green tea.

Finally, the rationale for use of green tea as an adjuvant in cancer therapy has been contradicted by recent clinical studies that demonstrated the inconsistent effect of green tea in preventing the occurrence of esophageal, stomach, liver, colorectal, and breast cancers.[12,13] In our opinion, it is a matter of public health to refrain from providing people with confusing information about the unproven therapeutic potential of tea derivatives without consistent information on their toxicity.

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To the editor:

Iron excess treatable by copper supplementation in acquired aceruloplasminemia: a new form of secondary human iron overload?

Ceruloplasmin plays a major role in iron mobilization from the tissues stores through its ferroxidase activity.[1,2] Hereditary aceruloplasminemia is an autosomal recessive iron overload disorder resulting from mutations in the ceruloplasmin gene.[3,4] Acquired hypoceruloplasminemia is observed in copper deficiency, which has been reported to cause anemia, neutropenia,[5] and, more recently, neurologic manifestations like myeloneuropathy with sensory ataxia and spastic gait.[6] We report here the first case of iron overload related to acquired aceruloplasminemia in a patient suffering from copper deficiency.

A 57-year-old male presented severe normocytic nonregenerative anemia (Hb 3 g/dL; normal range, 12-16 g/dL) associated to leukoneutropenia (1.3×10^3 leukocytes, normal range, $4\text{-}10 \times 10^3$; neutrophils 0.23×10^3; normal range, $1.5\text{-}7 \times 10^3$) with dysplastic marrow (dyserythropoiesis, hypogranular neutrophils, hyposegmented megakaryocytes), severe sensory gait ataxia, and a pure nephrotic syndrome (with minimal glomerular changes). Spinal cord MRI showed increased T2 signal involving the dorsal column. Corticosteroids were ineffective. Serum copper and ceruloplasmin concentration were markedly decreased at 0.2 μM (normal range, 12.5-24 μM) and 0.02 g/L (normal range, 0.18-0.6 g/L), respectively. Urinary copper excretion was low at 0.2 μM (normal range, 0-1.6 μM). The patient was treated during 4 months by oral copper supplementation. Responses of the hematologic, copper, and ceruloplasmin parameters were prompt and complete within 2 months. Proteinuria disappeared within 8 months. Neurologic symptoms improved gradually and, 3 years later, ataxia was no longer present.

A special diagnostic aspect was major iron overload syndrome with plasma ferritin 2687 μg/L (normal range, 55-345 μg/L) and hepatic iron concentration (magnetic resonance imaging [MRI]) 230 μmol/g (N < 36 μmol/g dry weight). In contrast, serum iron, transferrin saturation and total ferroxidase activity[7] were decreased at 4.3 μM (normal range, 12.5-25 μM), 8.6% (normal range, 23%-45%), and 0 IU/L (normal range, 482-614 IU/L), respectively. During follow-up, all biochemical iron parameters returned progressively to normal, including ferroxidase activity (443 IU/L). Liver iron overload decreased gradually and dramatically at MRI controls (60 μmol/g).

Severe copper deficiency was not due to chronic intestinal dysfunction. Whether it was related to zinc excess (zincemia was 21.3 μM, normal range, 12.5-18 μM), originating in the use of denture cream,[8] is a possibility. The role of the nephrotic syndrome toward copper deficiency[9] was unlikely because urinary copper was low and severe copper deficiency is not part of the usual clinical description of the nephrotic syndrome. Whether, conversely, copper deficiency played a causative role in the nephrotic syndrome remains an open issue. The present case revealed an interesting and novel situation of iron overload, related to acquired aceruloplasminemia. Hereditary aceruloplasminemia was ruled out on both genetic (no mutation was found in ceruloplasmin coding sequence) and family studies. The disappearance of iron overload under copper supplementation, with concomitant total restoration of plasma ferroxidase activity, represents a strong argument for attributing the iron disorder to aceruloplasminemia. Iron excess had no clinical expression in our patient. At variance with hereditary aceruloplasminemia, no MRI iron excess could be found within basal ganglia and no retinal degeneration was present.

Iron overload due to copper deficiency–related aceruloplasminemia represents a novel, easily treatable form of secondary iron excess, and provides further illustration of the close connection between iron and copper metabolism.[10]

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