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Case report

Hyperammonemia after high-dose chemotherapy and stem cell transplantation

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Summary:

We report a patient with multiple myeloma who suffered from hyperammonemia after a second stem cell autograft. This syndrome is not well known but is associated with a high mortality rate. Considering the possibility of this diagnosis in patients developing confusion and neurological degradation with respiratory alkalosis after intensive chemotherapy, could allow earlier treatment and perhaps improved survival. Possible mechanisms and potential therapies are discussed. With rapid recognition and treatment of the syndrome, the patient fully recovered. One and a half years later, she is still alive and well, on interferon for persisting myeloma. *Bone Marrow Transplantation* (2000) **26,** 343–345.

Keywords: peripheral blood stem cell transplantation; multiple myeloma; hyperammonemia

A 62-year-old Caucasian woman was a heavy smoker suffering from emphysema and ischemic cardiopathy. In February 1996, a diagnosis of IgA lambda multiple myeloma was made (IgA 29 g/l, Bence–Jones negative, multiple bone lesions on clavicles and skull). She was classified as stage IIIA according to the Durie and Salmon classification. She received seven courses of VMCP (vincristine, cyclophosphamide, melphalan and prednisolone) without a good response. Consequently, she was treated with four cycles of VAD (vincristine, doxorubicine, dexamethasone) followed by mobilization chemotherapy with cyclophosphamide plus etoposide to collect peripheral blood stem cells (PBSC) for two autotransplants. Before transplantation, she was in partial response (>50%). A first stem cell autograft was carried out in March 1997 after melphalan 200 mg/m^2 without any significant complication. She entered complete remission. Despite this, a relapse was observed 9 months later.

A second transplant was thus undertaken in February 1998. Conditioning consisted of TBI (6×2 Gy) and melphalan (140 mg/m^2). On day 5, the patient developed fever and dyspnea with bronchospasm. Broad-spectrum antibiotics including teicoplanine, imipenem, gentamicin and amphotericin B were unsuccessful. Several blood cultures yielded *Candida famata* and a chest CT-scan showed disseminated micronodules. 5-Fluorocytosine was started in addition to amphotericin B and the central catheter was removed. Two days later, blood cultures became negative, fever disappeared and the CRP returned to normal. Simultaneously, the patient developed mental confusion with respiratory alkalosis, which prompted her admission to an intensive care unit where tracheal intubation was necessary.

A cerebral CT-scan did not explain the confusion but an electroencephalogram showed a pattern compatible with metabolic encephalopathy. Arterial plasma ammonia concentrations were measured and revealed very high levels, ie >120 μmol/l (N < 40 mg/l). There was neither alteration of liver function nor other metabolic disturbances. A lumbar puncture showed an increase of glutamine and ammonia (102 μmol/l). Orotic acid was undetectable in the urine. A liver biopsy was performed and confirmed our suspicion of idiopathic hyperammonemia by showing microvesicular steatosis. Parenteral alimentation was discontinued to lower protein intake and treatment with lactulose, omeprazole and metronidazole was started. Additionally, we used carnitine (50 mg/kg/day) to promote urea production. Because a test dose of flumazenil, an antagonist of endogenous benzodiazepines, induced a spectacular awakening of the patient, she was also given a continuous infusion of the drug.

The patient was extubated on day 18 and treatment was continued until complete resolution of cerebral symptoms on day 35. She was discharged from hospital on day 43. She remained well afterwards without further therapy. Her multiple myeloma entered excellent partial remission (>90%). Maintenance treatment with interferon was started on day 180 but she showed evidence of moderate myeloma progression 1 year after the second transplant although no other treatment has been required so far apart from interferon maintenance. With a follow-up of 1$\frac{1}{2}$ years, she has remained well neurologically.

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Discussion

Idiopathic hyperammonemia syndrome has been previously described in BMT patients with an incidence as high as 0.5 to 1%.[1,2] It is defined as an elevated plasma ammonia concentration in the absence of significant liver function abnormalities. This syndrome has been described in patients receiving intensive chemotherapy for hematological malignancies (ALL, AML, CMML, MM) as well as after autologous or allogenic BMT or PBSCT (about 20 cases described).[1,2] Many cytoreductive drugs have been incriminated besides asparaginase or valproic acid which are known to produce hyperammonemia.[1,3] It usually occurs between 15 and 100 days after transplant when fever and neutropenia are present.[2] Our patient had a particularly early occurrence on day 5. Several explanations have been proposed for its more frequent incidence in leukopenic and febrile patients after chemotherapy.[4] First, severe infections during myelosuppression increase ammonia production via urease or other ammonia-generating enzymes. Second, mercaptans and short-chain fatty acids decrease the ability to create urea from ammonia in the liver. Finally, GI bleeding may also increase ammonia production and leukemic cells themselves could contribute to that production.

The syndrome has a rather atypic presentation, thus often resulting in a delayed diagnosis because there are many other possible causes (toxic, tumoral, infectious, metabolic or hemorrhagic) of confusion in immunosuppressed patients after chemotherapy for hematological malignancies. The principal manifestations are neurological with confusion, lethargy, cerebellar dysfunction that can evolve into seizures, encephalopathy and coma.[2,4–6] All patients have evidence of raised intracranial pressure but the exact mechanism is not known.[6] It could be a direct toxic effect of ammonia on intracranial blood vessels causing astrocyte swelling. Alternatively, it could be due to changes in cerebral metabolism by interference with cerebral respiration or accumulation of neurotransmitter substances, depletion of high-energy phosphates or change in cellular pH. Another possibility could be the accumulation of intracellular glutamine as described later.

These symptoms are accompanied by hyperventilation and respiratory alkalosis. The syndrome resembles Reye's syndrome or inherited defects of urea synthesis.[7] However, plasma amino acid and urinary orotic acid levels when measured did not show any argument for congenital urea cycle defects. Liver function tests are most often normal or only modestly abnormal.[2,4] Prothrombin time is normal.[2] Plasma and CSF ammonia levels are increased by definition. Arterial blood gases show respiratory alkalosis due to hyperventilation.

Neurologically, autopsies reveal astrocyte swelling and often herniation of cerebellar tonsils.[4] The white matter is often vacuolated.[8] These observations are in agreement with the fact that cerebral edema is a consequence of hyperammonemia.[2,9,10] Indeed, the cause of astrocyte edema is unknown but it could reflect the osmotic effect of accumulated intracellular glutamine which is the primary metabolic product of ammonia metabolism in the brain.[1] Glutamine synthetase, which is responsible for this, is located in astrocytes. Glutamine concentration is raised in the brain and cerebrospinal fluid in cases of idiopathic hyperammonemia and its level is associated with mental confusion as was the case with our patient. The liver may show centrilobular fatty infiltration, bile stasis and passive congestion.[11] The liver biopsy in our patient disclosed typical microvesicular steatosis. This differs from Reye's syndrome where the mitochondria appear abnormal. Finally, it is noteworthy to mention that a number of patients have GI bleeding demonstrated either clinically or at autopsy.[2]

Treatment of the syndrome first requires elimination of dietary nitrogen and suppression of intestinal ureolysis by lactulose and neomycin. Energy should be provided by concentrated glucose to minimize endogenous protein catabolism.[2,4] Tracheal intubation is often necessary for management of respiratory alkalosis.[2] This would allow creation of a pH gradient between blood and brain because at physiological pH, NH_3 is ionized to NH_4+ which is relatively lipid insoluble.[1] Dialysis is also effective for reducing ammonia concentration, but part of its beneficial effect may reside in the removal of urea precursors.[6] By analogy with congenital urea-cycle deficit, ammonia-trapping therapy has been used. Indeed, sodium benzoate or phenylacetate react with glutamine and glycine to form phenylacetyl-glutamine and hippurate which are excreted in the urine at a rate that approximates renal blood flow.[12] These metabolites are also cleared by hemodialysis.[11,13] Thus, ammonia production is decreased by diverting precursors.[1] As in our patient, L-carnitine can also be used because its administration prevents the neurological symptoms of acute ammonia toxicity by improving mitochondrial respiration and favoring ureagenesis.[14,15] Continuous infusion of flumazenil could also be recommended.[16] This drug is in fact an antagonist of benzodiazepine receptors and therefore could prevent the effect of endogenous benzodiazepines that are partly responsible for hepatic encephalopathy. Indeed, neurologic impairment in hepatic encephalopathy is commonly attributed to GABA-aminobutyric acid, the principal inhibitory neurotransmitter of the mammalian brain.[17] GABA is synthesized by gut bacteria and can induce an augmentation of the number of its own receptors in the brain. Furthermore, the receptor for benzodiazepines is one component of the GABA postsynaptic receptor. Several studies have shown clinical and electrophysiological improvement of hepatic encephalopathy by infusion of benzodiazepine receptor antagonists like flumazenil.[16,18,19] This suggests the existence of an endogenous ligand with benzodiazepine agonist-like properties but this has never been clearly demonstrated until now.[18] The mortality associated with the syndrome is over 50% despite appropriate therapy. It is very important to recognize the disorder very quickly to be able to start effective conservative management. With this strategy, it is possible to obtain complete and durable resolution of the syndrome.

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