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Introduction

During the last ten years, multiple new compounds have been introduced in the daily fight against cancer. In particular, today patients bearing lung cancer may benefit from therapy with pemetrexed, an anti-metabolite, and from biological therapies[1].

Pemetrexed is actually approved in combination with cisplatin for first-line treatment of malignant pleural mesothelioma[2] and for non-small cell lung cancer, histotype adenocarcinoma and large cells[1]. In this latter setting, it was demonstrated the superiority of pemetrexed both as monotherapy to docetaxel (second-line treatment)[1] and, in association with cisplatin, to cisplatin plus gemcitabine (chemotherapy-naive advanced patients)[3]. According to these results, on September 2008, the U.S. Food and Drug Administration approved pemetrexed in combination with cisplatin for the initial treatment of patients with stage IIIB/IV non-squamous non small cell carcinoma (NSCLC).

Unlike other antimetabolite drugs currently administered in cancer patients such as methotrexate and fluorouracil, which target a single enzyme, pemetrexed inhibits a larger number of enzymes that require folate, such as thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase[4].

Severe haematologic and gastrointestinal toxicities with several drug-related deaths were recorded in early trials[4]. The most important dose limiting side effects were neutropenia, mucositis and diarrhoea, whereas severe thrombocytopenia was recorded in less than 5% of the patients. These toxicities were greatly reduced by the introduction of folate and vitamin B12 supplementation.

Case description

We report the case of a 70 years old man that referred to our hospital in May 2012. He performed a thoracic and abdominal computed tomography (CT) scan, indicating the presence of a 6 cm right lung lesion and a brain nuclear magnetic resonance (NMR) pointing out two subtentorial metastasis.

The cytological exam from a fine needle aspiration of the lung lesion was diagnostic for a poorly differentiated non small cell carcinoma of the lung, T2 N0 M1 according to TNM classification.

Therefore, the patient started a first-line chemotherapy with cisplatin and gemcitabine ended in September 2012, with a complete brain response and lung mass stabilization. At the CT scan performed after 4 months, showed disease progression.

Patient conditions were good (performance status according to Karnofsky scale: 100%), thus a second line therapy with pemetrexed 500 mg/bsa every 21 days was proposed.

On February 2013, after folate and vitamine B12 supplementation, the patient received the first infusion (total amount of pemetrexed: 1000 mg). Concomitant therapies were: omeprazole (20 mg/day) and furosemide (25 mg/day), both started on May 2012. No anti-emetic therapy was administered. Baseline chemistry indicated (see Table 1): haemoglobin (Hb) 12 g/dl (nv: 13-17), platelet count (PLTs) 163.000/mcl (nv: 150-450), lactate dehydrogenase (LDH) 229 U/l (nv: 100-190) and bilirubin (BIL) 1.0 mg/dl (nv: 0.1-1.0).

Seven days after the start of chemotherapy neutrophil count was 840/mcl, with total white blood cells (WBC) count of 1460 cells/mcl, representing a typical hematologic toxicity grade III according to Common Toxicity Criteria version 4.0.

After 21 days, on 28th February, while WBC and neutrophil count recovered to normality, PLT count dropped down to 47.000/mcl, Hb decreased to 10.7 g/dl, LDH raised to 520 U/l, BIL was 1.7 mg/dl. We interpreted these values as permanent pemetrexed toxicity and we postponed the second cycle to the next week. On 6th March, Hb value was 9.9 g/dl, PLTs increased to 67.000, BIL remained stable to 1.67 mg/dl, and LDH decreased to 425 U/l.

According to the national guidelines to the use of hematopoietic growth factors, we prescribed recombinant erythropoietin alpha (40.000 units) that was administered on 7th March. Again, we postponed the therapy to the subsequent week. On 14th March, the patient referred to our Service.

He was pale and confused; the visit revealed evident icterus, a blood pressure of 150/90 mmHg with a heart rate of 90 beats/min. He presented a generalized dermal oedema which prevented any catheterization of a peripheral vein. Despite this difficulty, we collected a minimal blood sample that revealed Hb 7.1 g/dl, LDH 1110 U/l, PLTs 16.000/mcl and BIL 4.7 mg/dl mostly not conjugated; no external bleeding was evident. In the afternoon, a central venous catheter was positioned, giving us the possibility to start all the procedures for blood transfusion and plasma exchange. The new blood test revealed Hb 6.7 g/dl, PLTs 9.000/mcl, fibrinogen 424 mg/dl (nv 150-450), D-dimer 1183 ng/ml (nv: <270). Anisocytosis and poikilocytosis were found as unique features on peripheral blood smear. The patient died at 5 pm, before any hemocomponent transfusion. At autopsy, no bleeding or pulmonary embolism was evident; a moderate splenomegaly was found.

Discussion

The interpretation of this rapid and fatal evolution is rather complicated: the short time observation period (8 hours) and the difficulties to obtain blood samples prevented us to perform deeper analyses. However, we were able to record the following clinical characteristics: haemolytic anemia,

thrombocytopenia, elevated circulating D-dimer concentration with normal fibrinogen value, neurologic disorders and generalized dermal oedema.

Many drugs, including antimetabolite compounds like methotrexate and 5-fluorouracil, are known to cause drug-induced immune haemolytic anemia (IHA)[5]. Only two cases of IHA related to pemetrexed administration were reported in literature[6,7]. In the first case, Hb dropped from 9,7 g/dl to 4.3 g/dl in 20 days without any evident bleeding, platelet count was normal, LDH rised to 711 U/l, and anti-pemetrexed antibodies were indirectly revealed by in vitro tests.

Unlike this reported cases, the haemolysis of our patient started slowly, with a decrease in Hb concentration of 1.3 g/dl at first control (21 days after pemetrexed administration), and became dramatic in his last week, with a drop of serum proteins to 3.2 g/dl (total decrease from baseline to death: 5.3 g/dl).

Moreover, platelets consumption was evident from the beginning without modification in circulating fibrinogen level. Finally, we observed generalized dermal oedema, mental confusion and elevated D-dimer concentration, conditions never reported in IHA.

The thrombotic thrombocytopenic purpura syndrome (TTP), firstly described by Moschowitz in 1925, is a generalized disorder of the microcirculation. Clinically, TTP is characterized by haemolysis with evidence of schistocytes on blood smears, mental disorders or seizures, fever, thrombocytopenic purpura with possible cases of acute renal failure (the haemolytic uremic syndrome, or HUS). These manifestations are related to a microvascular thrombosis; thrombocytopenia is the consequence of platelets consumption, whereas erythrocyte fragmentation and haemolysis may be due to the contact between the red cells and the intravascular thrombi, causing a mechanical injury[8]. Several mechanisms, such as deficiency of ADAMTS 13 (a metalloprotease cleaving Von Willebrand factor)[8], a defective regulation of complement activation and toxins may all lead to microvascular thrombosis. What is still unclear is which are the

mechanisms that trigger this syndrome. TTP may occur after an infection with Shiga toxin produced by *E. coli* or *Sh. Dysenteriae*[9] or in association with conditions such as systemic lupus erithematosus or related autoimmune connective tissue disorders, drugs, pancreatitis, metastatic cancers and bone marrow transplantation; occasionally, TTP is not related to any evident plausible cause[9].

In the case here reported, symptoms and signs are more suggestive of a rapid, fatal TTP rather than an IHA, as platelet consumption and indirect signs of generalized thrombosis were present.

The aetiology of the syndrome of our patient is not clear. Neither symptoms suggestive for an infection such as hyperpyrexia, myalgia or diarrhoea were recorded nor new supportive drugs (i.e. antiemetics) were administered. Surely, TTP may have been triggered by the progressive metastatic disease. However, the time frame from pemetrexed infusion and symptoms onset is highly suggestive of a probable correlation between drug administration and TTP similarly to that already reported with gemcitabine[10].

Conclusion

Haemolysis, renal failure and schistocytosis on blood smear, typically associated to TTP were not evident. However, the rapid evolution of the syndrome may explain these discrepancies. We feel this observation of extreme interest because physicians should carefully monitor haemoglobin and platelets levels in patients receiving pemetrexed therapy keeping in mind the possibility of a rapid evolving, life threatening syndrome which require rapid medical intervention.

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Table 1.

Blood test values

	7th Feb	**14th Feb**	**28th Feb**	**6th Mar**	**14th Mar** (10 am)	**14th March** (2 pm)
WBC (x1000/uL)	5,13	1,46	11,8	6,8	3,58	3,62
Hb (gr/dl)	12	11,1	10,7	9,9	7,1	6,7
PLTs (x1000/uL)	163	145	47	66	16	9
GFR (ml/min)	53		60	67	66	
LDH (U/L)	229		520	425	1110	
Tot bilirubin (mg/dl)	1		1,7	1,67	4,7	
Direct bilirubin (mg/dl)	0,34		0,51	0,52	1,12	

Legend: WBC: white blood cells; Hb: haemoglobin; PLTs: platelet count; GFR: glomerular filtration rate; LDH: lactate dehidrogenase; INR: international normalized ratio.