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Case Report

Septic Shock on Post-Chemotherapy Febrile Neutropenia with Pneumopathy

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Abstract

Introduction: Febrile neutropenia is one of the most serious side effects of chemotherapy.

Case Report: We report a case of septic shock on post-chemotherapy febrile neutropenia on streptoccoccal pneumoniae in a 65-year-old woman with an oro-pharyngeal epidermoid carcinoma and broncho-pulmonary adenocarcinoma treated with chemotherapy. On admission, she is in acute respiratory failure in a febrile context with severe neutropenia at 0.5 x $10^{8/l}$ (50/mm3) progressing quickly to sepsis. The patient received oxygen by high concentration mask then noninvasive ventilation (NIV), vascular filling, broad spectrum antibiotics and immunomodulator. Despite all, the evolution is quickly towards a septic shock with renal failure and metabolic acidosis. In the face of a septic shock, the patient is intubated, ventilated in volume controlled mode in invasive mechanical ventilation and has required inotropic support of 1 m/hr of noradrenaline. Despite early care, she is died in a multivisceral failure state.

Conclusion: Febrile neutropenia is an oncological emergency with a mortality of > 10%. Most patients arrive with sepsis or septic shock state. Despite current therapeutic advances, the prognosis remains pejorative.

Keywords: *Neutropenia; Chemotherapy; Sepsis*

Introduction

Febrile neutropenia is one of the most serious side effects of chemotherapy. Indeed, 10 - 50% of patients with a solid tumor and more than 80% of patients with malignant hematopathy will develop post-chemotherapy febrile neutropenia with a 5 - 11% mortality [1-3]. We report a case of post-chemotherapy neutropenic fever on pneumopathy. The evolution is rapidly towards a septic shock and visceral failure.

Case Report

This is a 65-year-old woman who was followed in oncology for recurrence of broncho-pulmonary adenocarcinoma TTF1 negative (Thyroid Transcript Factor1), initially treated in 2016 by radiotherapy and currently treated by immunotherapy and chemotherapy (carboplatine/alimta et pembrolizumab) and an oro-pharyngeal epidermoid carcinoma treated with induction chemotherapy by three cycles of TPF (T = docétaxel, P = cisplatine, F = 5-fluorouracile) relayed by radiation therapy associated with ERBITUX. She is addressed to the

Emergencies for acute respiratory distress in a febrile context and is immediately admitted into a progressive care unit. The clinical examination at admission showed asthenia, altered general condition, 38.6° fever, and severe undernutrition (BMI 15.8). Neurologically, it is somnolent but without any neurological localization sign or neurological deficit. About the cardiovascular system, the heart sounds are normal without a sign of heart failure. There is a low blood pressure = 76/40 mmhg with average blood pressure = 52 mmhg, sinus tachycardia = 146/mn and weak peripheral pulse. Concerning respiratory status, she's dyspneic, polypneic at 30/min with thoraco-abdominal asynchrony, bronchial congestion with predominantly right-sided hypoventilation and pulse oximeter oxygen saturation (SPO_2) 80% under 10 l/min of oxygen in the high concentration mask. The digestive system is normal. Renal function is impaired with anuria. About the cutaneous, it presents mottling and cyanosis of the extremities, absence of oedema.

MASCC score (Multinational association for supportive care in cancer) = 10 (high-risk patient). QuickSOFA = 3 (drowsiness, hypotension and polypnoea). SOFA score (Sepsis-related Organ Failure Assessment) = 9 points with mortality risk (15 to 20%). Electrocardiogram showed sinus tachycardia, with no evidence of repolarization disorder. Chest X-ray showed condensation syndrome without pleural effusion (Figure 1).

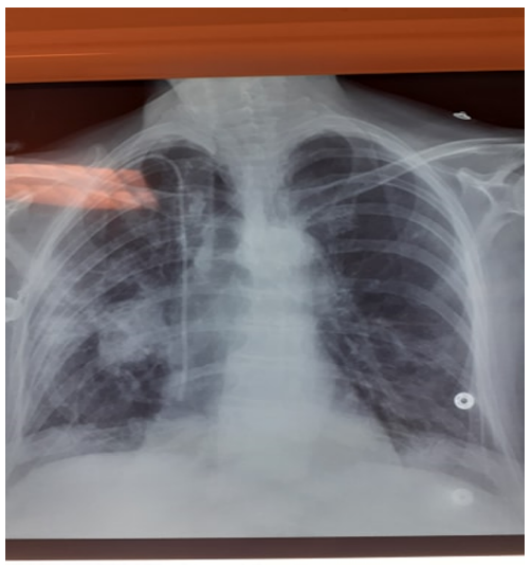

Figure 1: *Chest X-ray.*

Here are the results of the biological tests:

- Arterial blood gas (ABG): PH = 7.33, $PC0_2$ = 44 mmhg, PO_2 = 77mmhg, HCO_3^- = 22.6 mmol/l, excess base = -2.8 mmol/l, alkaline reserve = 23.9 mmol/l (hypoxemia and metabolic acidosis).
- Kidney function test: creatinine = 279 µmol/l, urea = 22.57 mmol/l and MDRD clearance: 15.72 ml/mn and glomerular filtration rate (GFR) = 14.72 ml/min (acute renal failure probably functional).
- Inflammatory biologic syndromes and sepsis marker: CRP = 705 mg/l, lactate = 4.61 mmol/l, procalcitonin = 100 ng/ml (Sepsis).
- Haemogram: hemoglobin = 10.8 g/dl, hematocrit = 32.2%, MCV = 101.3µ^3, Total leukocyte count (TLC) = 110/mm^3 (0.11g/l) with 0.5 x 10^8/l (50/mm^3) of neutrophils, Platelet = 25000/mm^3 (25g/l) (Leukopenia, neutropenia, thrombocytopenia).

- Coagulation test: PT = 20.4s (51%), INR = 1.63, PTT = 46.7s.
- Blood electrolyte test: Sodium = 132 meq/l, potassium = 4.1 meq/l.
- Liver function test: Total bilirubin = 2.2 mg/l (3.7 µmol/l), SGOT ou ASAT = 20 U/l, SGPT ou ALAT = 14 U/l, GGT = 110 U/l, alkaline phosphatase = 41 UI/l.
- The bacteriological examination is in progress (blood culture).

Immediate treatment consisted of oxygen therapy by mask at a high concentration of 15 l/min, vascular filling by plasmalyte 1000 ml in 03h and Nacl 0.9% 1000 ml in 03h, antibiotic with tazocillin 4 g x 2 in 24h and amikacin 1500 mg in 24h, an immunomodulator by zarzio (Filgrastim) 30 MU and a digestive antisecretory by inexium 40 mg.

The immediate evolution is marked by the persistence of hemodynamic disturbances (BP: 76/40 mmhg, HR = 138/mn) and signs of shock (mottling, cold extremities, weak peripheral pulse). On the respiratory side, dyspnea is persistent with polypnea, thoraco-abdominal asynchrony, $SP0_2$ at 86% and cyanosis. For renal function, the anuria persisted. The evolution towards septic shock is observed. we set up noradrenaline in electric syringe pump started at 1 mg/H, liquid supply by NaCl 3000 ml/24h, corticosteroid therapy with solumedrol 60 mg and non-invasive ventilation (AI = 13 cmH_2O, PEP = 5 cmH_2O, Fio_2 80%).

Evolution at D1 is marked by stable hemodynamic status under norepinephrine at 4 mg/h (BP: 110/65 mmhg). Episode of sinus tachycardia sustained at 200 beats/mn rapidly reduced by administration of tildiem 12.5 mg IV (Figure 2). Respirationally, the evolution is marked by the installation of a severe acute respiratory distress syndrome (ARDS) with $Pa0_2/Fio_2$ = 30, hypoxemia (PO_2: 24 mmhg), hypercapnia (PCO_2: 77 mmhg) and mixed acidosis (pH: 7, HCO_3: 18,16 mmol/l). Neurologically, the patient fell into a coma with a Glasgow score of 7/15 without any neurological localization sign or neurological deficit; the pupil is intermediate reactive. For renal function, there is oliguria at 600 ml in 24h with creatinine 296 µmol/l (clearance 14.68 mL/min). In terms of haematology, there is persistence of thrombopenia at 2000/mm^3 and leukopenia at 140/mm^3 with neutropenia at 0.64 x 10^8/l (64/mm^3). Blood cultures came back positive for *Streptococcus pneumoniae*, which is sensitive to tazocillin and amikacin. In the face of this situation, the patient is intubated and put on controlled ventilation. We set up a sedation by hypnovel at 2 mg/H and fentanyl at 50 mg/H. we have continued the noradrenaline at 4 mg/H, liquid supply by Nacl 0.9% 1500 ml/24 and polyionique serum 1000 ml/24h. We set up Lasilix 40 mg, tazocilline 4g x 2 per 24h, zarzio 30 MU per 24h, inexium 40 mg per 24h, solumedrol 60 mg per 24h, paracetamol 1g x 3 per 24h. Hemodialysis is scheduled with the resuscitation team, but the patient is dead in a multivisceral failure.

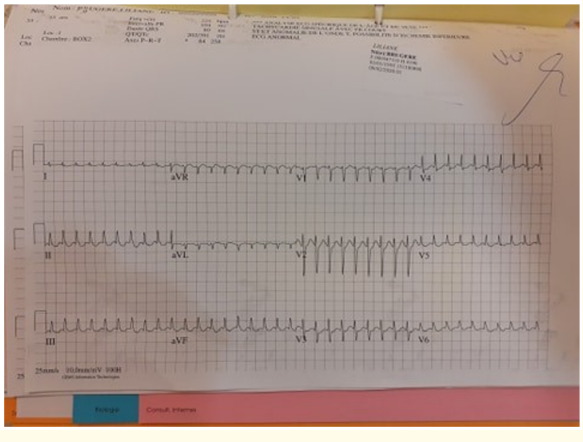

Figure 2: *Sinus tachycardia sustained*

Discussion

Despite progress in its prevention and treatment, febrile neutropenia remains a serious and frequent complication of cancer chemotherapy. His prognosis depends directly on the quality of the initial treatment. According to the Infectious diseases society of America (IDSA), febrile neutropenia (NF) is defined as an oral temperature ≥ 38.3°C in a single dose or ≥ 38°C for a duration > 1 hour associated with a neutrophil count (PNN) < 0.5 x 10^9/l or may become so in the next 48 hours [1]. For the European Society of Medical Oncology (ESMO), it is a fever > 38.5°C in a single measurement or > 38°C in two measurements at an interval of two hours associated with a neutrophil count < 0.5 x 10^9/ l [2]. Our case fits this definition, fever at 38.5° and leukopenia at 110/mm^3 (0.11g/l) with neutropenia at 0.5 x 10^8/l (50/mm^3) in a patient undergoing chemotherapy for two different cancers notably bronchopulmonary adenocarcinoma and oropharyngeal squamous cell carcinoma. The incidence of fever is 10 - 50% for neutropenia lasting less than 5 - 7 days and over 90% for neutropenia lasting more than 7 - 10 days [4]. In the emergency department, 45% of patients with NF have criteria for severe sepsis or septic shock [5]. In our case, we do not know how long neutropenia settles because it is discovered during the initial test in face of febrile respiratory distress with pneumopathy. The criteria for sepsis and septic shock were observed within hours of admission to the progressive care unit. For the initial assessment, we used 03 scores, including the SOFA, QSOFA to determine sepsis-related organ failure and the MASCC score to assess the risk of complications. So our patient was in severe sepsis (QSOFA at 3 and SOFA at 1) and classified at high risk of complication (MASCC at 10). Effectively in the literature [6], the MASCC score is recommended because it makes it possible both to determine the risk of complication or mortality and to guide management. Management is based primarily on antibiotic therapy, and regardless of the MASCC score, the first dose of antibiotic should be given within one hour of arrival in the emergency department. In a high-risk patient (MASCC < 21) like our patient, management is carried out in a hospital environment, or even in an intensive care unit [3,7,8]. Bacteriologically, in our case, the blood cultures came back positive for *Streptococcus pneumonia* and the infective site was only pulmonary. According to some authors, until 1990, Gram-negative bacilli were the most common. With the increasing use of implantable venous catheters in oncology and the administration of fluoroquinolone antibiotic prophylaxis during chemotherapy with the risk of prolonged neutropenia, Gram-positive coccis are currently responsible for more than 50% of infections. At the same time, antibiotic resistance is increasing and multi-resistant bacteria are emerging: extended-spectrum betalactamases (ESBLs), methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) [3,9,10]. In our case, the bacterium identified was *Streptococcus pneumoniae*, which is sensitive to the antibiotic administered on admission. Some authors have described that fast-growing atypical *Mycobacteria* (*Mycobacterium chelonae* and *Mycobacterium fortuitum*) can occasionally be isolated from infections related to central catheters [10]. For other authors, fungal infections can also cause severe clinical pictures and are associated with high mortality. *Candida* and *Aspergillus* are the most frequently incriminated but that's not the case in our study [2,11]. About management, an empirical broad-spectrum intravenous antibiotic should be administered immediately, and consists of monotherapy with a betalactamine which also covers *Pseudomonas aeruginosa*. These may be tazocillin, carbapenems (imipenem or meropenem) or cefepime [4,8,9]. Combinations may be necessary in certain situations to broaden the spectrum of the antibiotic and achieve a synergistic effect. For us, due to the high risk, the patient is immediately hospitalized in progressive care and put on tazocillin 4g x 2 per day and amikacin 1500 mg. According to some studies, prophylaxis with G-CSF (Granulocyte-colony stimulating factor) is effective in reducing the risk of NF during chemotherapy. During an episode of NF, G-CSFs are not recommended as a first-line treatment. In cases of severe sepsis or prolonged neutropenia, they may be indicated [12-14]. In other studies, the initiation of growth factor therapy to treat an already present infection ("curative G-CSF") appears to have limited clinical benefit [15,16]. In our case, we used Filgrastim 30 MU/d because the patient is in sepsis with severe neutropenia, but it did not seem to be effective. Concerning the optimization of respiratory function, our patient was put on oxygen by high concentration mask on admission but it does not seem to be effective. Afterwards she was put on noninvasive ventilation (NIV) but still not effective. In front of an ARDS, the orotracheal intubation with controlled ventilation was adopted. According to some authors, respiratory complications are common in neutropenic patients and often progress to acute respiratory failure, as observed in our case [17,18]. Early management of acute respiratory failure in the intensive care unit is associated with lower mortality [18,19]. Controversies have been observed in relation to the use of mechanical ventilation. Several studies have suggested a benefit in terms of use of intubation, incidence of complications and survival with the use of non-invasive ventilation (NIV) as a first-line treatment in oncohematology patients with bilateral pulmonary

infiltrates [20-22]. However, this benefit has been fickle demonstrated in other studies [23]. More recent cohorts report a decrease in mortality in ventilated oncohematology patients [24,25]. A recent randomized study found no benefit associated with the use of NIV in this patient population [26]. Thus, it no longer appears permissible to recommend the routine use of first-line NIV for hypoxemic respiratory failure in this patient population. NF-related mortality ranges from 3.8 to 9.5% [7], from 1% in low-risk patients [2] to 14% in high-risk patients [27], and up to 50% in patients admitted to intensive care [7]. Factors contributing to poor prognosis include: delayed initiation of a broad-spectrum antibiotic, the depth, duration, and speed of onset of neutropenia, certain infectious foci (pneumopathies, dermohypodermatitis, extensive buccopharyngeal infection, and perineal infections), and organ failure [2,6]. For us, in spite of the precocity of the management as well as the measures of resuscitation, the patient died 48 hours after her admission related to multivisceral failures, in particular, renal insufficiency, ARDS and acidosis. about the mortality linked to sepsis or septic shock during an NF, other authors have found the following result: mortality in intensive care 40.1%, hospital mortality 49.8%, mortality at 6 months 63.3% [28].

Conclusion

Febrile neutropenia is an oncologic emergency with > 10% mortality. The majority of patients present with criteria for severe sepsis or septic shock. Prompt management with adequate antibiotic therapy within one hour of arrival at the emergency room reduces morbidity and mortality. The MASCC (Multinational association for supportive care in cancer) score classifies patients into two groups, those at low risk (PBR) and those at high risk (PHR) of complications. In spite of the advances in treatment, the prognosis remains pejorative.

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Volume 6 Issue 5 May 2020