

# Spontaneous remission of acute myeloid leukaemia after recovery from sepsis

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## ABSTRACT

Spontaneous remission of acute myeloid leukaemia (AML) is extremely rare and usually of short duration. We report two patients with documented AML who developed spontaneous remission of their leukaemia shortly after an episode of severe sepsis and respiratory failure requiring mechanical ventilation. The underlying mechanisms of spontaneous remission remain unclear but an association with preceding blood transfusions and severe systemic infections has been reported. An overwhelming immune response due to sepsis and leading to raised levels of TNF- $\alpha$ , INF- $\gamma$ , IL-2 and an increased activity of NK cells, cytotoxic T-cells and macrophages are thought to play an important role. Better insights into the mechanisms of spontaneous remission of AML after recovery from sepsis could help in developing new therapies for AML.

## KEYWORDS

Acute myeloid leukaemia, critically ill, immune response, mechanical ventilation, sepsis, spontaneous remission

## INTRODUCTION

Treatment of haematological malignancies is still accompanied by a high therapy-related morbidity and mortality rate.<sup>1</sup> If admission to an intensive care unit (ICU) is indicated because of respiratory failure, it often predicts a poor prognosis with a mortality rate of 60 to 90%.<sup>2,3</sup> This high mortality rate is mainly due to multiple organ failure as a result of severe sepsis caused by opportunistic infections related to prolonged neutropenia. In addition, administration of chemotherapy is often postponed until patients are discharged from the ICU, resulting in an important delay in the treatment of the underlying disease, which also affects the prognosis negatively. For these reasons, there

is much controversy about whether or not patients with haematological malignancies should be admitted to the ICU when they require mechanical ventilation. Here we describe two patients with acute myeloid leukaemia (AML) who were given the benefit of the doubt and were admitted to our ICU because of severe sepsis and respiratory failure in the very beginning of their illness, just before or just after the diagnosis of AML was made. The clinical course showed an unexpected and surprising twist leading to a spontaneous remission of the AML.

## CASE REPORTS

Patient A, a 29-year-old Iraqi male, was transferred to our hospital in September 1997 because of a suspected AML. Laboratory results showed a mild leucocytosis of  $12 \times 10^9/l$ , with 21% blasts. Bone marrow biopsy showed an AML, classified as French-American-British (FAB) M2. Cytogenetic analysis of the bone marrow demonstrated a t(8;21) translocation and deletion of the Y chromosome. Two days after admission, a superimposed infection was suspected and the patient was immediately treated with broad-spectrum antibiotics (cefpirom), and chemotherapy was postponed. After three days, progressive respiratory failure developed, showing bilateral infiltrative abnormalities on a chest X-ray. He was transferred to our ICU and mechanical ventilation was started. According to our protocol, empiric antifungal (itraconazole) and antiviral (aciclovir) therapy was added to broad-spectrum antibiotics (imipenem-cilastatin). Microbiological examinations, including repeated broncho-alveolar lavage (BAL), gave no additional diagnostic clues. The patient was intermittently ventilated in prone position for two weeks. Mechanical ventilation was complicated twice by an acute tension pneumothorax. Laboratory tests showed a persistent pancytopenia, necessitating frequent

transfusions with erythrocytes and platelets. Over time, the patient's clinical condition deteriorated with development of severe cachexia, and the clinical picture of an ongoing sepsis. Extensive microbiological examinations yielded no causative micro-organism. Three weeks after admission to the ICU, a spontaneous rise in the white blood cell count and platelets heralded a dramatic improvement in the patient's clinical condition, resulting in successful weaning off the ventilator followed by extubation. A repeated bone marrow examination showed a hypercellular bone marrow without the presence of blasts, suggesting a spontaneous cytological remission of the AML. This was confirmed cytogenetically by a normal karyogram without t(8;21) translocation and the presence of a normal Y chromosome. A few days later, he was transferred to the haematology ward. Bone marrow examination was done repeatedly and showed a persistent cytological remission (<5% blasts) which was confirmed by polymerase chain reaction (PCR). The patient refused a consolidation course with chemotherapy and unfortunately, after three months, PCR again showed the presence of (8;21) translocation and after six months, bone marrow examination also showed a cytological relapse of the AML. During the second induction chemotherapy according to the HOVON protocol ([www.hovon.nl](http://www.hovon.nl)), the patient died of a massive intracranial haemorrhage.

Patient B, a 28-year-old Dutch male, was admitted to the ICU in January 2006 because of a septic shock. The patient's history revealed no prior diseases. He complained of having a sore throat and fever for one week and had developed diffuse bruising of his skin. The patient was seen in the emergency room of another hospital and a diagnosis of streptococcal infection was suspected. On admission, we saw a critically ill young man with high fever up to 41°C and an altered mental state. He complained of headache, fatigue and dyspnoea. On physical examination a petechial rash and bruising of the skin was seen on the trunk and lower parts of the body. He was haemodynamically unstable with a systolic blood pressure of 80 mmHg. Laboratory tests showed a pancytopenia with a white blood cell count of  $1.3 \times 10^9/l$ , Hb 5.0 mmol/l and thrombocytes of  $33 \times 10^9/l$ . The differential showed 26% blasts. Blood gas analysis showed a mild respiratory alkalosis, initially without hypoxia. Sepsis in combination with an acute leukaemia was suspected. He was treated with broad-spectrum antibiotics (imipenem/cilastatin). After a few hours his clinical condition deteriorated with progressive respiratory failure and mechanical ventilation was started. Blood cultures revealed group G  $\beta$ -haemolytic *Streptococci* and penicillin G was administered. Bone marrow aspirate showed an acute monoblastic leukaemia, classified as FAB-M5B, without chromosomal abnormalities. According to our protocol, antifungal (voriconazole) and antiviral (aciclovir

and gancyclovir) therapy was added empirically. As a result of the patient's septic condition, cytostatic drugs were not applied. Transfusions with erythrocytes and platelets had to be given every other day. The clinical course was further complicated by a leucocytoclastic vasculitis of the skin, and a central venous catheter related bloodstream infection. Two weeks after admission, a spontaneous rise in white blood cell count and platelets developed. Surprisingly, the repeated bone marrow examination showed a complete cytological remission of the AML. The condition of the patient improved remarkably and he was extubated shortly after spontaneous remission was confirmed. The patient was transferred to the haematology ward and received remission-induction chemotherapy followed by myeloablative allogeneic stem cell transplantation without noticeable complications. Unfortunately, four weeks after he was transplanted, a full-blown relapse of the AML was diagnosed.

## DISCUSSION

Spontaneous remission (SR) of AML is rare in adults. Since the first description in 1878<sup>4</sup> about 100 cases have been reported.<sup>5</sup> SR became even more infrequent when effective therapeutic strategies for acute leukaemia became widely available. SRs in AML are of short duration (mean 7.7 months; range 1 to 36); however, long-term remissions and even complete cytogenetic remissions have been documented.<sup>6</sup> The mechanisms inducing SR are thought to be diverse and may partially be mediated by cellular immune phenomena, but remain unclear in most cases.<sup>7</sup> An association of SR in AML with preceding transfusion of blood products and/or concomitant infections has been noted.<sup>8</sup> Mostly bacterial, but also fungal or viral infections are observed. Infections have been argued as triggering an immune response causing SR. In particular severe systemic infections appear to precede SR.<sup>5,7,9,10</sup> Severe sepsis is characterised by a profound increase in cytokine levels such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-2 (IL-2) and interferon- $\gamma$  (IFN- $\gamma$ ) as well as an increase in natural killer (NK) cells and cytotoxic T cells. Also hypergammaglobulinaemia is frequently seen in these patients<sup>5,8,11-14</sup> and might suggest a potential role of humoral immune events in SR: increased antibody-mediated cytotoxicity of NK and cytotoxic T cells and of activated macrophages due to better recognition, opsonisation or adhesion could play a role in this phenomenon.<sup>9</sup> In our two patients, the presence of a severe systemic inflammation could have played an important and possibly a causal role in developing the observed SR.

The association between transfusions of blood components and SR has been reported.<sup>5,8,12-14</sup> Cytotoxic antibodies against leukaemic cells, and allogeneic lymphocytes

might play a role, representing mechanisms similar to those described as graft-versus-leukaemia (GVL) effect in allogeneic transplanted patients.<sup>15</sup> However, at present, neither of the theories have been proven and nearly all AML patients receive multiple leucocyte-depleted transfusions, usually without achieving SR.

It can be hypothesised that overwhelming sepsis leading to an exuberant activation of the immune system causes containment of the leukaemia. This mechanism is used as a paradigm for designing new antileukaemic therapies. For instance TNF- $\alpha$ , a cytokine that regulates cell proliferation and differentiation, and takes part in the immune response, has been demonstrated to cause inhibition of blast cell proliferation *in vitro*.<sup>13,16,17</sup> Promising effects of IL-2 have already been shown in patients with refractory or relapsed AML who were not suitable for further chemotherapy or as postconsolidation therapy after induction chemotherapy.<sup>18,19</sup> The principle of using the immune system to fight the cancer is being investigated in solid tumours, lysing tumour cells or preparing tumour specific peptides, followed by uptake of tumour antigens by dendritic cells and presentation to the immune system.<sup>20</sup> Based on this mechanism, several groups are trying to refine the method of antigen presentation, for example by dendritic cell vaccination.<sup>21</sup> However, these studies are still preliminary and further large randomised trials are needed to address this issue.

Although it would be very intriguing to solve the puzzle about SR in AML, prospective studies regarding this issue are difficult to carry out. The rarity of this phenomenon asks for a multicentre approach, and the complexity of the situation asks for a systematic approach, determining all possibly involved factors (cytokines etc), so that the culprit can be pinpointed and used for targeted therapy. All this has prevented such a study from actually taking place, so that we only have case reports to help us in solving the causative mechanism of SR in AML, but these have given us ideas about causative factors which are now being investigated.<sup>13,16-21</sup>

## CONCLUSION

We have described two patients diagnosed with AML who were admitted to our ICU because of severe sepsis and respiratory failure requiring mechanical ventilation. Despite clinical deterioration and a predicted poor prognosis, SR of the AML occurred. SR in AML is very rare but it has been reported before. It is in particular associated with severe infection, although this association is hard to prove. Soluble factors such as TNF- $\alpha$ , IL-2, INF- $\gamma$ , hypergammaglobulinaemia, cross-reactive antibodies, direct cytotoxic antibodies in donor serum as well as cellular factors such as an elevated number of NK cells or allogeneic lymphocytes with a GVL effect in blood transfusions have been considered

to be involved in SR. Nevertheless, the exact mechanisms of SR still remain unclear. Though most remissions are of short duration, long-term remissions and even complete cytogenetic remissions have been documented. Better insights into mechanisms underlying spontaneous remission could help us to develop new therapeutic approaches.

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