# Late differentiation syndrome in acute promyelocytic leukemia: a challenging diagnosis

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## Abstract

Detailed knowledge about differentiation syndrome (DS) has remained limited. There are 2 large studies conducted by the Spanish workgroup PETHEMA (Programa Español de Tratamientos en Hematología; Spanish Program on Hematology Treatments) and the European group trial (LPA 96-99 and APL 93) in which the incidence, characteristics, prognostic factors and outcome of patients developing DS are evaluated. Both have described the median time of DS development between 10 and 12 days. The severity of the DS has been evaluated in the study conducted by PETHEMA, and severe DS usually occurs at the beginning of the treatment (median of 6 days), as compared with moderate DS (median of 15 days). We report here in two cases of late severe DS, with late diagnosis due to both time and form of presentation. We discuss the physiopathology, clinical presentation, prophylaxis and treatment of DS.

## Introduction

The differentiation syndrome (DS) is the main life threatening complication of the acute promyelocytic leukemia (APL) treatment with all trans retinoic acid (ATRA).

The incidence of DS varies between 2 to 27%.[1] This variation is mainly due to different diagnostic criteria used among studies.[2-5]

The symptoms/signs that should lead high to suspicion of DS include dyspnea, edema, unexplained fever, hypotension, pulmonary infiltrates in chest radiography, pleuro-pericardial effusion, weight gain higher than 5 kg and/or vascular leak syndrome leading to acute renal failure.[1] However, the diagnosis is mostly based on the presence of the above clinical and/or radiological criteria and supported by the response to early therapy to corticosteroids. In addition, some authors consider that if 4 or more of the above-referred symptoms were present, the diagnosis would be severe DS.[3] The differential diagnosis should always include lung infection, sepsis, thromboembolism and heart failure, and is more challenging when time of presentation isn't the expected.

The median time to the development of symptoms after ATRA treatment varies between 2 to 21 days, with a median period of 10 days. The PETHEMA (Programa Español de Tratamientos en Hematología; Spanish Program on Hematology Treatments) trial identified two types of DS,[1] named *early*, when it occurs within the first 7 days after starting ATRA, and *late* DS if the syndrome is developed after the first 7 days. In the same PETHEMA trial, the presence of hypotension, unexplained fever, pericardial effusion and renal failure were associated with late and severe DS. Although the development of severe DS is still associated with a considerable increase in morbidity and mortality during induction (nearly 1% in most studies) the suspicion and the early treatment with corticosteroids have significantly reduced the mortality rate of this complication.[1]

In the present article we report two cases of late severe DS, with late diagnosis due to both time and form of presentation.

## Case Report

The first patient, a 53 years old man, was diagnosed of high risk microgranular variant APL, presenting gingivorrhagia and fever. Anemia (Hb: 7.8 g/dL), more than $10\times10^9$/L leucocytes ($11.8\times10^9$/L), and thrombocythopenia (platelets: $2.75\times10^9$/L) were present as well as coagulopathy (prothrombine time: 54%; fibrinogen: 114 mg/dL). The bone marrow aspirate showed infiltration by 93% of promyelocytes, and 80% of them were hypogranular. The diagnosis was confirmed by conventional cytogenetic, FISH and molecular studies, identifying the t(15,17) and *PML/RAR* (bcr3) isoform.

The patient was included in the LPA 2005 PETHEMA protocol and received idarrubicin, 12 mg/m$^2$ on days 2, 4, 6 and 8 and ATRA, 45 mg/m$^2$ since day 1. According to the protocol, the patient received dexamethasone at dose of 5 mg/12 hours during 15 days as DS prophylaxis because of leucocytes count at diagnosis was $>5\times10^9$/L.[6]

Twenty-four hours after stopping dexamethasone, when he had just recovered from neutropenia (neutrophils: $1.2\times10^9$/L), the patient developed fever without any clinical focus or microbiological documentation. Although wide spectrum antibiotics (piperazilin-tazobactam and teicoplanin) were administered, febrile syndrome was maintained. Six days later, on day 22, with neutrophil counts of $2.8\times10^9$/L, the patient developed hemodynamic instability with maintained hypotension, tachycardia, tachypnea and oliguria with fluid retention, respiratory insufficiency and evidence of hepatic failure. The chest radiography showed bilateral alveolar infiltrates and venocapillary hypertension signs. The patient was admitted to the Intensive Care Unit (ICU), requiring invasive mechanical ventilation and vasoactive drugs. At that moment, in absence of any microbiological documentation, late DS was suspected and ATRA was discontinued. Dexamethasone was administered and significant clinical and radiological improvement was observed 4 days after initiation. After complete recovery, ATRA was reintroduced without further complications. Eight months after achieving molecular complete remission (CR), the patient relapsed with central nervous system involvement, and promyelocytic infiltration was detected in the cerebrospinal fluid analysis. Rescue therapy, that included arsenic trioxide (ATO) plus intrathecal liposomal cytarabine, leaded to achievement of molecular remission and the patient received allogeneic stem cell transplantation. At the present time, he remains and disease free, 20 months after transplantation. The second patient was a 56 years old lady, diagnosed of low risk APL based on laboratory investigation due to hemorrhagic diathesis and fever. At diagnosis she presented anemia (Hb: 7.8 g/dL), leucopenia ($0.4\times10^9$/L)

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and thrombocytopenia (platelets: $46\times10^9$/L). The bone marrow aspirate showed 38% of blasts, all of them abnormal promyelocytes, and the diagnosis was confirmed by cytogenetic and molecular analysis, detecting t(15,17) and *PML/RAR* (bcr1) isoform, respectively.

She was also included in the LPA 2005 PETHEMA protocol and received idarrubicin 12 mg/m$^2$ days 2, 4, 6 and 8 and ATRA 45 mg/m$^2$ since day 1. Since it was classified as of low risk, no DS prophylaxis was required.

Seventeen days after treatment initiation, the patient developed fever with no clinical focus and no microbiologic documentation. Wide spectrum antibiotics (piperacilin/tazobactam, teicoplanin and amikacin) were administered without improvement. At day +22, when granulocyte count started to recover ($0.350\times10^9$/L), the patient evidenced crepitants on right pulmonary base, without dyspnoea or cough. Bilateral pulmonary infiltrates were observed in thorax X-ray and the computerized tomography reported the presence of bilateral pulmonary opacities, with areas of unpolished glass. This was radiologically suggestive of fungal infection and empiric treatment with B-amphotericin, cotrimoxazol and oseltamivir was given together with enlarged spectrum antibiotics.

Seven days later, on day +28, the patient developed respiratory failure with dyspnea, requiring large debit oxigenotherapy. Intensive care unit admission was required, requiring non-invasive mechanical ventilation. At that time, DS was suspected and ATRA was discontinued starting treatment with dexamethasone at dose of 10 mg twice per day. Forty-eight hours later, significant improvement was observed, with disappearance of fever and respiratory symptoms. ATRA was reintroduced during the consolidation without any further complications.

## Discussion

The introduction of ATRA for the treatment of APL has been one of the most significant advances in the management of hematologic neoplastic diseases. APL is, at the present time, the most curable form of adult myeloid leukemia, reaching a 5-years disease free survival of 70-80%.[7-11] However, DS is probably the most significant ATRA-related toxicity.

The median time of DS presentation is 10 days. Here we report two late DS, developed on day +22 in both cases. Although late DS has been reported by Montesinos *et al.*[1] analyzing two PETHEMA studies (LPA 96 and LPA 99) by the PETHEMA group (0-46 days) and by the European group (1-35 days),[2] the median time of presentation was not in any study superior to 12 days. In the first case the patient had leucocytosis at diagnosis and he received dexamethasone as DS prophylaxis according to the protocol. This fact could have contributed to the delayed development of DS because the febrile syndrome with respiratory compromise and hypotension appeared four days after steroids discontinuation, and at that time the patient had already recovered from neutropenia, which made DS less probable. In the second-one case, the patient was not previously treated with prophylactic dexamethasone due to low risk classification, but the symptoms were coincidental with recovery from aplasia, which lead us to first suspect of a granulocyte recovery-related symptomatology. It was due to progressive clinic deterioration with respiratory symptoms that we first suspect of DS.

Prophylactic use and duration of corticosteroids stills controversial, and in fact, our first patient received prophylaxis with dexamethasone but he developed later DS, leading us to question its utility. LPA 96 PETHEMA protocol recommended the prophylactic administration of steroids during 7 days; the LPA 99 protocol extended this recommendation to 15 days, and the current protocol, LPA 2005, indicates prophylaxis in all patients with more than $5\times10^9$/L during 15 days. In our case, though the prophylactic therapy prevented the DS during the first 15 days of treatment and the syndrome started just after corticosteroid discontinuation, making us to question if in high-risk patients it would be useful to keep corticosteroids during all induction treatment. Corticosteroids might prevent pulmonary infiltration of APL cells via reduction of the alveolar chemokine secretion and thereby might prevent the development of DS.[12] However, due to the fact that dexamethasone does not reduce the chemokine production by differentiating APL cells it may be less effective during treatment of installed DS,[12] so its utility seems to be more evident as prophylaxis than when DS is developed.

Although the impact of administration of dexamethasone in mortality rate is not well supported in different studies,[1,3] our patients developed severe DS according to the PETHEMA criteria,[1] and it is well recognized this fact as related with higher mortality: 27% *vs* 7% in patients with severe DS *vs* no severe DS, respectively.[1]

Concerning the question if the use of prophylactic corticosteroids in all patients is advantageous this should be settled in randomized studies, also considering the use of corticosteroids less toxic than dexamethasone, *i.e.* prednisone, taking into account its potential efficacy in this setting and that infectious complications did not apparently increased with its use.[13]

There is no consensus about the presence of risk factors predicting the development of DS. Some studies found no associated risk factors,[2,13-15] while others suggest that the white blood cells count at diagnosis and during induction can be the only important risk factor.[1,3]

Analysis of PETHEMA studies identified other risk factors in a series with more than 700 patients with APL such as abnormal serum creatinine,[1] *FLT3*-ITD mutations, hypogranular variant (M3v), short *PML/RARα* isoforms, and male gender.[1] CD13 expression was also correlated with DS in other study.[11] The first patient here reported presented leukocytosis at diagnosis, and in addition, he was a male who had also the hypogranular variant of APL. However, the second one had no any previous risk factors predicting DS but the syndrome was evident twenty-two days after ATRA initiation, just when she was recovering of neutropenia.

Finally the mortality of DS is currently very low (1%), mostly due to early corticosteroids treatment, together with the concomitant use of chemotherapy associated to ATRA.[2,11] However the development of this complication has been associated with other complications, such as increase in morbidity and extramedullary relapses.[1,2,8,16,17] In our first patient, extramedullar relapse at CNS occurred, eight months after molecular CR achievement. One hypothesis is that this is related with ATRA-induced modulation of adhesion molecules. If DS is a syndrome of tissue infiltration by maturing myeloid cells it is easy to understand how certain sanctuary sites may be capable of withstanding the antileukemic effect of consolidation chemotherapy.[8]

## Conclusions

In conclusion, DS is a relatively frequent and serious complication in patients with APL, and the time of presentation can largely vary. We should consider DS in all patients with unexplained fever during the ATRA treatment, regardless of the time of presentation. Although the prophylaxis with steroids, through the reduction of incidence of severe DS, could have an indirect impact in the mortality rate of APL patients, its use in all patients should be settled in randomized trials.

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