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An uncommon triad of myelodysplastic syndrome, Crohn's disease and autoimmune hepatitis: A case report and review of the literature

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ABSTRACT

Myelodysplastic syndrome (MDS) is associated with an autoimmune disease (AD) in 10 to 20% of cases. Crohn's disease (CD) is not a common autoimmune manifestation reported with MDS. The triad made up of MDS, CD and another autoimmune manifestation is even more unusual. To our knowledge, only four cases with this triad have been reported in the literature to date, and ours is the fifth. It's about a 50-year-old man with a history of autoimmune hepatitis who was diagnosed, five years later, with MDS with multilineage dysplasia. He was started on Azacitidine three weeks before retaining the diagnosis of an associated CD.

Introduction

Myelodysplastic syndrome (MDS) is a clonal disease of the hematopoietic stem cells resulting in hypercellular dysplastic bone marrow, ineffective hematopoiesis and therefore peripheral single or multiple cytopenias [1,2]. A considerable occurrence of MDS across several autoimmune disease (AD) types has been demonstrated by many studies [3]. They may herald, co-occur or succeed autoimmune manifestations [3]. Indeed various immune manifestations have been currently reported among MDS patients with variable incidences [4]. However, concurrent cases of MDS and Crohn's disease (CD) which is an inflammatory bowel disease (IBD) are rare [5].

The triad made up of MDS, CD and another autoimmune manifestation is even more unusual. To our knowledge, only four cases have been reported in the literature. The present case is therefore the 5th one.

Case presentation

A 50-year-old man presented to our outpatient Hematology Department in August 2019 with pancytopenia. He had a 5-year history of definite autoimmune liver disease, with a score of 7 according to the International Autoimmune Hepatitis Group's simplified criteria [6] . On physical examination, His WHO status performance index [7] was 0. The patient had no palpable peripheral adenopathy, hepatomegaly or splenomegaly. He had no bleeding. Laboratory data revealed pancytopenia with macrocytic nonregenerative anemia (hemoglobin:9.5 g/dl, MCV:107 fl, reticulocytes: 67 000/mm3), leukoneutropenia (leukocytes: 2310/mm3, neutrophils: 780/mm3) and thrombocytopenia (platelet: 48 000 mm3/L). Peripheral blood smear showed no blasts at that time.

Thus, diagnostic procedures aiming at excluding reactive cytopenias were performed and were negative. Vitamin B12 and folate levels were normal. On abdominal ultrasound the liver and the spleen were of normal size.

A bone marrow aspirate was therefore performed and showed trilineage myelodysplasia with a normal cellularity, 5% of myeloblasts without ringed cells. Bone marrow Karyotype revealed poor cytogenetic abnormalities with presence of monosomy 7 and additional Y chromosome on all mitoses analyzed. The diagnosis of MDS with multilineage dysplasia was then made based on the 2016 WHO classification [8]. The R-IPSS (Revised International Prognostic Scoring System) [9] was 7.5 compatible with a very high risk of leukemic transformation.

Three weeks later, and before starting treatment with Azacitidine, the patient was admitted in the gastroenterology department for proctalgia and alternating episodes of constipation- non-bloody diarrhea in a context of altered general condition. The diagnosis of CD involving the ileum and the colon was thus retained based on typical colonoscopy and histological findings. The patient was started on prednisolone (1 mg/kg/day) with alleviating of gastrointestinal symptoms.

Prior to hospital discharge, a blood count was performed and showed leukocytosis with aggravation of anemia and thrombocytopenia: leucocyte count: 37 230/mm3, hemoglobin: 6 g/dl, platelets: 31,000/mm3. Peripheral blood smear showed 45% of blasts.

A bone marrow aspirate confirmed the diagnosis of acute myeloid leukemia (AML). The patient was given a 3 + 7 induction regimen with

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Cytarabine (200 mg/m^2, IV continuous infusion over 24 h during 7 days) plus Daunorubicin (90 mg/m^2, IV bolus during 3 days). One month later, he died because of pulmonary infectious complications.

Discussion

MDS is a disorder affecting the bone marrow stem cells [1,2]. It is characterized by dysmyelopoiesis affecting erythroid, myeloid and megakaryocytic lineages at variable degrees [1,2]. The association between MDS and AD has been reported by several studies, with a frequency of 10 to 20% [10,11]. A Swedish study showed a higher risk of developing MDS in patients with a history of AD compared to the general population [12]. Although their association appears to be more than coincidental or fortuitous, little is known about whether one disease is partly responsible for the development of the other [13,14]. The most commonly reported autoimmune manifestations with MDS are seronegative arthritis, recurrent polychondritis and cutaneous vasculitis [15]. None of the four reported cases nor ours had any of these usually described autoimmune manifestations as shown in Table A.

IBD is a group of disorders that affect the digestive tract and cause chronic inflammation. It includes CD and ulcerative colitis [16]. They are considered as specific body organ AD, although some authors have expressed some doubt based on the fact that in the case of IBD and specifically CD, the autoimmune system attacks healthy bacteria present in the gastrointestinal tract instead of attacking a part of the body [3,17,18]. The association of IBD with MDS has been more reported with ulcerative colitis while concurrent CD and MDS cases are scarce [5,19].

Anemia, which is the most common circumstance of the discovery of MDS among patients diagnosed with IBD is commonly seen in patients diagnosed with CD [20]. It may be due to iron deficiency, malabsorption of folic acid and vitamin B12, or may be therapy-related [5,21].This may delay or make difficult the diagnosis of an associated MDS. Thus, it is in the case of unexplained persistent anemia or associated cytopenia(s) that the diagnosis of MDS should be evoked.

To date, only four cases with a triad made of MDS, CD and another AD have been reported in the literature, and ours is the fifth (Table A).

The chronology of the onset of these entities is variable. Indeed, immunological disorders may rarely precede the diagnosis of MDS by several months to years such as in cases n°3 and ours [4,22]. The most adopted explication here is therapy-related MDS [3,23]. In fact, immunosuppressive therapies used to treat AD are known to have a carcinogenic potential but with no proven correlation between the duration of drug exposure and the risk of myeloid neoplasms [24]. Among these drugs, the carcinogenic potential has been broadly described with alkylating agents and topoisomerase II inhibitors and to a lesser extent with anti-metabolites [25,26]. However, no one of the two patients received any immunosuppressive drug.

In other cases, MDS may characterize the initial clinical presentation of this association as seen in cases n°1 and 4 (Table A). Here, the autoimmune clonal proliferation of T-cells and the excessive secretion of TNF-a, interleukin 1, and interleukin 6 by monocytes as described in MDS patients may play a role in the development of autoimmune conditions [27,28]. It could lead to an abnormal lymphocytic response that contributes to additional immunosuppression and so to the development of AD [5].

In case n°2 (Table A), AD and MDS were diagnosed concomitantly. The hypothesis of the existence of a common immunologic process seems then very plausible [5]. While AD affect adults younger than 30 years old with a second peak occurring after 60 years of age, MDS is a disease of the elderly diagnosed in more than 80% of cases in patients over 60 years old [17,29]. The average ages of the onset of AD and MDS in the cases reported in Table A were 61.8 (range: 44–80) and 65.8 years (range: 50–74), respectively. Four out of the five patients were males, which is in line with MDS but not with AD [30,31]. It appears thus that AD if associated with MDS may have an unusual gender distribution.

Three patients (cases n° 1,2 and ours) underwent cytogenetic examination. Their karyotypes are mentioned in Table A and correspond to intermediate, good and poor cytogenetic prognostic subgroups, respectively. For note, few reports have suggested an association between concurrent occurrence of CD and MDS or leukemia with chromosomal abnormalities [32]. However, the only two constitutional chromosomal abnormalities identified to have an increased risk for both hematologic disorders and IBD are Turner and Hermansky-Pudlak syndromes [13]. These anomalies were not described in our case series.

An attempt to correlate AD and MDS subtypes based on the French-American-British classification revealed that refractory anemia with ring sideroblasts (RARS) was the most common subtype [1]. Nevertheless, these findings are limited by the small series samples and the lack of previous comparison with a large control group of MDS without AD [4,11,33]. No one of the patients in this study has an MDS type of RARS. However, refractory anemia was reported in 3 of the 5 cases.

CD involved the colon in four patients, the anus in one patient and the ileum in two cases. For note, a more frequent colonic involvement is unusual in CD and has been more reported with older age at disease onset (27,34). This is consistent with the findings of our serie.

As for autoimmune manifestations, the patients we report have all received anti-inflammatory drugs made of steroids only or associated to 5-aminosalicylic acid (5-ASA) like in cases 2 and 3 (Table A). Their autoimmune symptoms were satisfactorily managed. Theoretically, they remain poorly controlled in most cases despite significant advances in their treatment [17]. All the more, their therapeutic approach when associated to MDS is not yet codified [17]. It is therefore important to mention that treatments of MDS, especially Azacitidine, showed efficacy on signs of AD [10,11]. However, responses of MDS to steroids used to treat autoimmune conditions are variable and cases of improved, refractory or even worsened cytopenias have been registered [4,11,35,36].

Thereby, only one of the patients reported (case n°4) received chemotherapy made of Etoposide. However, cases 2, 3 and ours benefited from supportive care only. The only satisfying option reported for MDS management is hematopoietic stem cell transplantation (HSCT) [3]. Interestingly, it is actually also considered as an effective option in treating severe or refractory AD including CD through reconstituting the hematopoietic system and restoring immune function as well [37].

As for the evolution of MDS, two of the five cases developed into AML after 12 and 18 months of myelodysplasia's diagnosis respectively. In fact, although AML is a common complication of MDS, especially in patients with high R-IPSS scores, data reported in the literature suggests that associated AD increases the incidence of progression to AML [38]. However, the overall survival is not affected by this association nor by the type of AD [11]. The only proven survival factors are MDS characteristics including IPSS score, WHO classification and cytogenetic findings [11]. Survival times are available for four of the five patients. They range from one to 60 months after the diagnosis of MDS, with an average of 25 months. It was 18 months in our case [34].

Conclusion

In conclusion, in the case of IBD, especially CD, anemia should be carefully managed and myelodysplasia should always be considered in case of moderate to severe persistent anemia or associated cytopenias. All the same, diarrhea in patients with MDS should draw attention to a possible associated IBD. However, the coexistence of extra-intestinal autoimmune manifestations is exceptional but possible making the treatment decision more challenging.

Ethical committee approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from a legally authorized representative for the anonymized patient information to be published in this case report.

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CRediT authorship contribution statement

Arij Cheffai: Writing – original draft, Writing – review & editing. **Wiem Boufrikha:** Methodology, Supervision, Validation. **Rim Rakez:** Conceptualization, Supervision, Validation. **Amina Ben Ghechir:** Resources. **Mohamed Adnène Laatiri:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendices

Table A
Summary of cases reported in the literature of associated MDS, CD and another AD, with our case.

N	Author/ Reference	Sex	Age at diagnosis of the 1st AD	Age at diagnosis of MDS	CD location	Other Autoimmune manifestation	Type of MDS (WHO classification)	Karyotype	Autoimmune manifestations' treatment	MDS treatment	MDS evolution	Survival (months)
1	Yoshida et al. (39)	M	69	67	Ileum	pyoderma gangrenosum+ sterile osteomyelitis	RA	46,XY,+1, der(1,7) (q10,q10)	Steroids	–	AML	60
2	Sahay et al. (21)	M	71	71	Colon	Pyoderma gangrenosum	RA	Not done	Steroids, 5-ASA	Supportive measures	RAEB	21
3	Sahay et al. (21)	M	44	66	Colon	Immune complex mediated glomerulonephritis	RA	Normal	Steroids,5-ASA, Metronidazole	Supportive measures	unspecified	unspecified
4	Hebbar et al. (27)	F	80	74	Colon, anus	psoriasis	RAEB-T	Not done	Steroids	Etoposide	unspecified	1
5	Our case	M	45	50	Ileum, colon	autoimmune hepatitis	RCMD	46, XY, $+Y$, -7	Steroids	Supportive measures	AML	18

RA: refractory anemia.
RAEB: refractory anemia with excess blasts.
RAEB-T: refractory anemia with excess blasts in transformation.
RCMD: refractory cytopenia with multilineage dysplasia.
5-ASA: 5-aminosalicylic acid.

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