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Surgical and Experimental Pathology (2022) 5:8
https://doi.org/10.1186/s42047-022-00110-0

Surgical and Experimental Pathology

CASE REPORT

Open Access

Monocytosis and Multiple Myeloma: treatment-related acute leukaemia?

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Abstract

Background: Therapy-related acute monocytic leukemias in patients with plasma cell dyscrasias are infrequent.

Case presentation: We here present a case of a 60 year old female who developed an acute monocytic leukemia two years after the diagnosis of multiple myeloma. She was treated with an alkylating agent and bortezomib before undergoing a hematopoietic stem cell transplantation. She suffered of multiple severe infections until her immune system was adequately reconstituted. A year afterwards, she presented signs of deterioration unrelated to the MM, with pancytopenia. The bone marrow aspirate failed to show a prominent blast population. The diagnosis of AML was confirmed after a bone marrow biopsy.

Discussion: The development of acute leukaemia after treatment for multiple myeloma is a well characterized phenomenon. Most frequently, patients develop a myelomonocytic leukemia. Similarly, synchronous acute myeloid leukemias are myelomonocytic or myeloblastic. Rarely synchronous AMLs are monocytic. The development of such suggests a dysfunctional bone marrow microenvironment.

Keywords: Multiple myeloma, Leukaemia, Alkylating agents, Bortezomib

Background

Multiple myeloma (MM) is a clonal and multifocal neoplastic proliferation of plasma cells (PCs) (McKenna 2017). It is a clinicopathological diagnosis. According to the revised International Myeloma Working Group criteria, the diagnosis of MM is made when: 1) bone marrow plasma cells are more than or equal to 10% or there is a plasmacytoma confirmed by biopsy in bone or extramedullary tissue, and 2) it is accompanied by MM defining events such as: a) end organ damage due to the proliferative disorder or/and b) identification of biomarkers including a light chain serology and imaging studies (Kumar et al. 2017; Vincent Rajkumar et al. 2014).

With these criteria in mind, the reported annual incidence varies by country. Its annual incidence is higher in more-developed countries (Kumar et al. 2017). Reports on Latin America identify MM as second to non-Hodgkin lymphomas in prevalence. The prevalence in Mexico is of 27.1% as of 2019. The mean age at diagnosis is of 60 years of age. Contrary to patients in more-developed countries, patients diagnosed with MM in Latin America often have comorbidities at diagnosis, the most frequent being chronic metabolic diseases. Despite an increase in diagnostic techniques and survival rates, patients in Latin America present with advanced disease, with an International Scoring System at diagnosis of III (de Moraes Hungria et al. 2020; Tietsch de MoraesHungria et al. 2006; Hungria et al. 2017; Hungria et al. 2019; Vargas-Serafin et al. 2021).

Myelomagenesis is characterized by genetic and epigenetic alterations, clonal evolution and the interplay of the microenvironment and the neoplastic plasma cells. It is

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a long process that includes chromosomal translocations affecting genes, including IGH, aneuploidy, hypermethylation of DNA as well as acquired mutations that allow tumor progression (Kumar et al. 2017).

Treatment for MM patients is determined by two variables: eligibility for autologous hematopoietic stem cell transplantation (AHSCT) and risk stratification. Initial therapy for those eligible for AHSCT include bortezomib, lenalidomide, dexamethasone (VRd) and, alternatively, daratumumab, lenalidomide, and dexamethasone (DRd). For those ineligible for AHSCT, VRd and DRd are recommended, discarding melphalan-based regimens due to concerns on stem cell damage, secondary myelodysplastic syndrome, and acute leukemia. Nonetheless, the preferred treatment for conditioning for AHSCT in those classified as high risk is melphalan. On the other hand the treatment of choice for relapses depends on many factors, the first of which is refractoriness to lenalidomide followed by the timing of the relapse, response to prior therapy, aggressiveness of the relapse, and performance status. For patients who are not refractory to lenalidomide, multiple triplet regimens are considered. In patients who are refractory to lenalidomide, options for therapy at first relapse consist of several pomalidomide-based or bortezomib-based combinations (Rajkumar and Kumar 2020).

In Latin America, the three most used chemotherapy treatments in patients who received an AHSCT include a Thalidomide-based treatment, a Bortezomib-based treatment and a combination of cyclophosphamide, thalidomide and dexamethasone (CTD). Patients who do not receive a bone marrow transplantation most often receive either a thalidomide-based treatment, melphalan, thalidomide plus steroid or melphalan plus steroid. In Mexico, both, patients who receive AHSCT and those who do not, are often treated with a thalidomide-based therapy (Hungria et al. 2019).

Experience demonstrates that many Latin American countries have not been able to add novel agents as first-line therapy against MM. Likewise, from those eligible for transplantation, around half undergo AHSCT. Thus, the overall survival rate of both eligible and non-eligible AHSCT patients can be further increased with addition of novel therapies.

Although the most relevant problem in Latin America is not therapy-related complications but logistics, considering the increasing survival rate Latin America has demonstrated in the last few years (Hungria et al. 2017; Hungria et al. 2019), the former is probably the focus of years to come.

Leukemia is the most frequent therapy-related malignancy (Higgins and Shah 2020; Leone et al. 2001). Its incidence has increased as a product of a longer life expectancy and higher rates of survivorship. Therapy-related myeloid neoplasms (t-MN) include therapy-related acute myeloid leukemia (t-AML), myelodysplastic syndromes (t-MDS), and myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN) (Arber 2017). They are secondary to the use of alkylating agents or the use of topoisomerase inhibitors (Leone et al. 2001). The latency varies but it is usually after years of treatment; for MM, most have reported more than two years of treatment (Higgins and Shah 2020; Mailankody et al. 2011). The dose, age and addition of radiation are considered risk factors. In t-MNs secondary to therapy with alkylating agents, AML is preceded by a myelodysplastic syndrome (MDS) and the latency is of 5 to 10 years (Arber 2017; Nadiminti et al. 2021). The effects these drugs have on the DNA have been the accepted explanation since first described. However, individual predisposing factors have been better characterized with time, making this entity another example, though more precocious, of the sum effect of the hallmarks of cancer (Higgins and Shah 2020).

As for plasma cell neoplasms, t-MNs are increasingly recognized as long-term complications, including alkylating chemotherapy, specially melphalan (Leone et al. 2001). Reddi et al. demonstrated that complex abnormalities and -5q / -7q cytogenetic abnormalities were present in 79% of their patients with MM and later t-MN having a direct correlation with the use of melphalan-based chemotherapy regimens, with the highest risk for regimens melphalan-cyclophosphamide combinations (Reddi et al. 2012). Observational studies of hematological malignancies have shown an increased risk of MNs after autologous transplantation with intravenous melphalan-based conditioning (Radivoyevitch et al. 2018). The five-year cumulative incidence of t-MN after transplantation and maintenance with lenalidomide is 0.7% (Jones et al. 2016). Likewise, post-transplant maintenance with drugs derived from thalidomide such as lenalidomide, also increase the risk of t-MN and MDS as it magnifies the risk due to previous exposure to oral melphalan. According to a meta-analysis by Palumbo et al., the combination of lenalidomide plus oral melphalan significantly increased the risk of hematological second primary disease (HR 4.86 [95% CI: 2.79– 8.46]) (Palumbo et al. 2014). So far, there is no clear data to support the increased risk of MPD or t-MN with the use of bortezomib (Leone et al. 2001; Reddi et al. 2012; Radivoyevitch et al. 2018; McNerney et al. 2017; Gertz et al. 2015).

Since first described, the most frequent t-MN in MM patients are both acute myeloblastic and acute myelomonocytic leukemia (Leone et al. 2001; Kyle et al. 1970; Bierbach et al. 1979). We here present a case report highlighting a t-MN with a distinct phenotype.

Case presentation

A 60 year old female patient was referred to our Institute after a monoclonal gammopathy was identified. She had no relevant past medical nor social history. The patient presented weight loss, back pain, weakness and fatigue, night sweats, and pallor. Complete blood count (CBC) showed severe anemia, leukopenia and thrombocytopenia, as well as, hypercalcemia, alterations in renal function and the presence of Bence Jones protein in urine. The imaging studies showed generalized lytic lesions and several pathologic fractures. Measurement of antibodies showed hypergammaglobulinemia with lambda restriction. The bone marrow aspirate (BMA) demonstrated infiltration by plasmatic cells in 80% and the bone marrow biopsy showed a diffuse infiltration of the interstitium by neoplastic plasmatic cells with light chain restriction (Fig. 1). The neoplastic population was positive to CD138, CD38 and CD56. Multiple myeloma was confirmed.

She was treated with six cycles of cyclophosphamide, bortezomib and dexamethasone. The last cycle was modified to thalidomide, bortezomib and dexamethasone. During the chemotherapy, she developed several severe infections, including latent tuberculosis, bacteremia due to *Streptococcus mitis*, and persistent *Clostridioides difficile* infection (four relapses in total). After a dose of melphalan, she received an AHSCT after 6 months of treatment.

The following years, she continuously developed severe infections including a disseminated infection with *Mycobacterium avium* and a urinary tract infection by ESBL producing *E. coli*. There were no clinical nor serological signs of residual disease. However, the patient endured with anemia and a mild leukopenia.

Two years after the AHSCT, she developed bleeding gums, epistaxis, petechiae, and ecchymoses. She also referred weakness, fatigue, headaches, bone pain and weight loss. The patient arrived at the emergency department due to symptoms and signs of heart failure, which was discarded. The CBC showed a pancytopenia, with hemoglobin of 9.7 mg/dL, white blood cells of 2,270 and platelets of 31,000. The pancytopenia could not be explained by chronic infections. She was hospitalized for diagnostic work up.

There were no serological signs of relapse of multiple myeloma. The imaging studies did not identify any changes. A BMA was performed and showed a homogenous population of cells measuring approximately 16 um, with basophilic cytoplasm, irregular nuclei, some bean-shaped, with one or two nucleoli. This population accounted for 22% of the cells. The cytomorphology proved compatible with immature hematopoietic cells. However, the immunophenotype did not show a clonality for monocytes.

A bone marrow biopsy was performed, which showed a cellularity of 70% with 50% of the cells characterized by a larger size, with abundant cytoplasm, an indented nuclei with vesicular chromatin, distributed at the interstitium (Fig. 2a-b). The rest of the hematopoietic population showed no features of dysplasia; no myeloid blast cells were observed. Plasmatic cells were identified with mature morphology and a perivascular distribution. The immunohistochemistry showed the neoplastic cells were positive for monocyte-specific antigens (Fig. 2c-f).

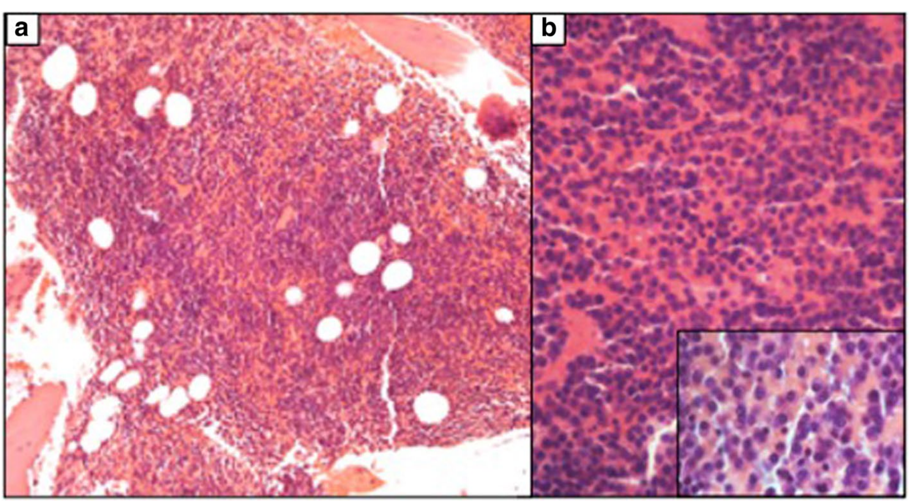

Fig. 1 **a** Bone marrow with diffuse Interstitial infiltration of mature and immature plasma cells (H&E 4x); **b** Plasmatic cell detail, round eccentric nuclei with cart-wheel chromatin and variable nucleoli (in set), with abundant basophilic cytoplasm (H&E 20x, 40x)

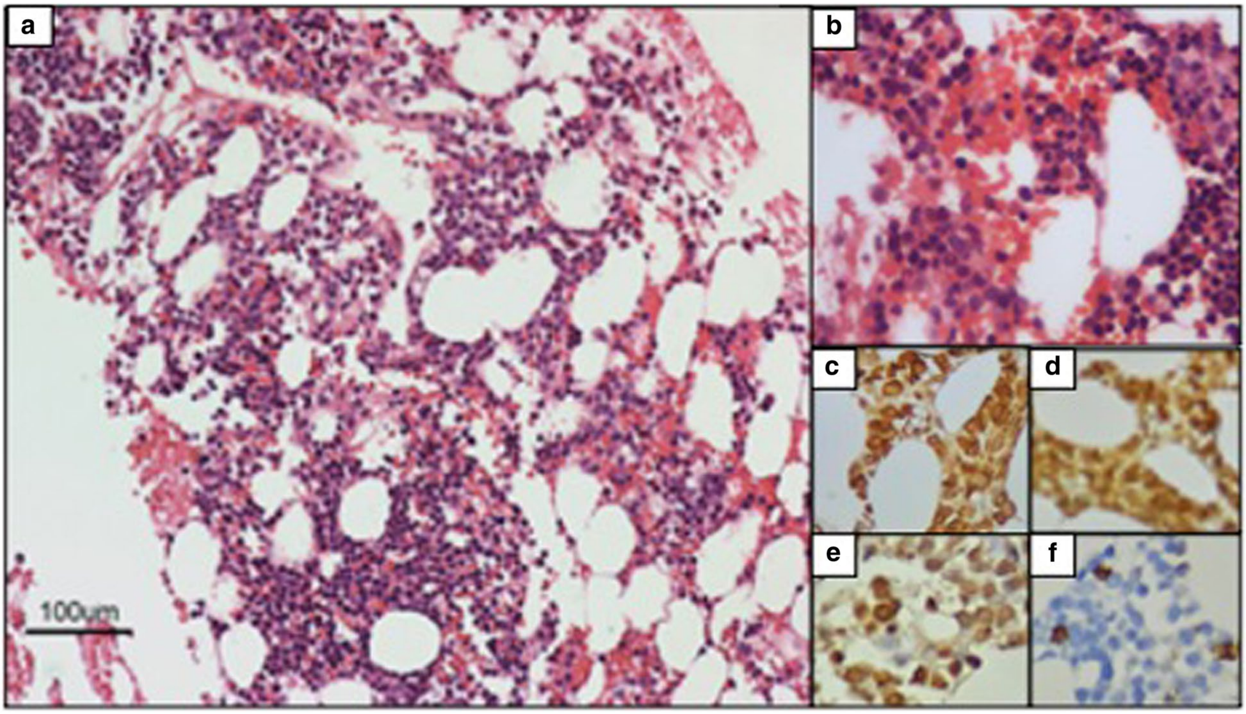

Fig. 2 **a** Hypercellular bone marrow with interstitial distribution of monocytoid cells and perivascular mature cells; **b** Monocytoid cell detail; **c** CD163 (+) **d** CD68 (+) **e** lysozyme (+) **f** CD117 (-)

A new BMA was performed, this time demonstrating maturation arrest in myeloid cells, a 28% blast cell count, with the following immunophenotype: CD64+, CD15+, CD13+, CD33+, CD4+(Fig. 3). No complex cytogenetics were identified. Mutations for IDH, CBF-beta, FLT3 and NPM1 were negative. Thus, a diagnosis of acute monocytic leukemia was made.

Analysis of mutations in TP53 were done taking DNA from both the bone marrow biopsy where the diagnosis of MM was confirmed and where the AML was diagnosed three years afterwards. A Sanger sequencing was used to identify mutations in exons 5 to 10. A non-sense mutation in exon 6 was identified in the plasmatic cell neoplasm; no mutations were identified in the myeloid neoplasm.

The patient received chemotherapy based on Venetoclax and cytarabine; however, the disease progressed substantially. She has experienced multiple severe infections and constantly requires transfusions. She is now in palliative care.

Discussion and conclusions

We performed a thorough search for simultaneous and treatment-related acute monocytic leukaemias in patients with MM. A total of 28 case reports and case series were retrieved; after examining the criteria used for classifying the acute myeloid leukaemia, the articles were narrowed to 16, with 13 case reports and 2 case series, with a total of 23 patients (Table 1).

From the twenty-three cases retrieved, five were t-MNs and fifteen were simultaneous MNs (Kyle et al. 1970; Bierbach et al. 1979; Raz and Polliack 1984; Akashi et al. 1991; Kim et al. 2010; Shi et al. 2015; Levinson et al. 2002; Osserman 1971; Naparstek et al. 1982; Luca and Almanaseer 2003; Marcović et al. 1974). All of the reported M5's had a monocytic phenotype, unlike the simultaneous M5, with three of them having a monoblastic phenotype. Interestingly, none of the t-MNs had a medical history of hematological disorders, opposite to the cases of synchronous MM and AML M5, with several reporting myelodysplastic disorders.

Most of the patients in both groups were men. They had a median age of 68.5 when diagnosed with MM, and most had an IgG kappa gammopathy, with few having IgA or IgM. As for the treatments received, all the t-MNs received at some point melphalan, in combination with cyclophosphamide, steroids and/or radiotherapy. Comparable to our patient, a common finding was monocytosis in the CBC. All the patients had a dismal evolvement.

The clinical presentation in cases with synchronic MM and AML included non-specific symptoms (weakness, fatigue, pallor and weight loss). A common finding in the

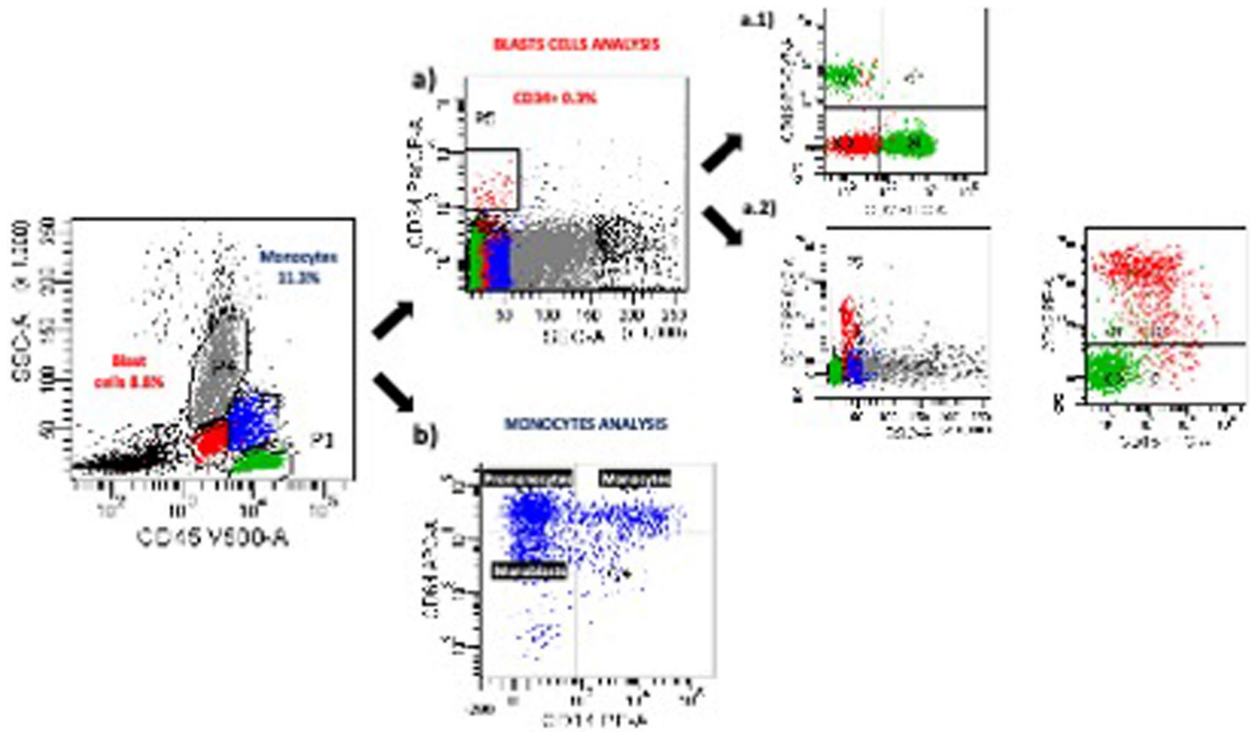

Fig. 3 Bone Marrow Immunophenotypic Analysis. **a** Blast Cells Analysis (CD45 low) solely 0.3%, not meeting criteria for acute leukemia. **a.1** Blast do not express T o B lymphocyte markers. **a.2** Expression of myeloid markers (CD 117 +, CD13 +), also expressed by monocytic lineage. **b** Monocytes Analysis (CD45 high): Promonocytes (CD64 high, CD14 Neg) and monoblast (CD64 Neg, CD14 Neg) prevalence, both considered blast equivalent

CBC was anemia, sometimes accompanied by thrombocytopenia. Analogous to t-MNs, monocytosis was the rule; and, despite treatment, patients deteriorated rapidly.

Though the first t-MN reported in the literature was made by professor Elliott F Osserman on 1967, who for years studied MM among other hematological diseases, pure acute monocytic leukaemias secondary to treatment are very few (Kyle et al. 1970). Osserman was the first to suggest that development of a leukemic clone in patients with MM may be due to therapy or due to recurring infections. In the same line, MM may impose a decreased immune surveillance and, consequently, AML may develop. The simultaneous presentation of MM and AML has raised the possibility of a proximate ontogenetic relationship between plasmatic cells and myeloid cells (Osserman 1971; Naparstek et al. 1982; Luca and Almanaseer 2003). In fact, an isolated case report confirmed the biphenotype of the myeloid cells and the myeloma cells of a 77 year old male patient with simultaneous MM and AML. The myeloid cells isolated from peripheral blood showed expression of B cell markers (CD10 in 95% while CD20, CD19 and CD21 were < 5%) and T cells markers. Through immunohistochemistry, they found some myeloid cells staining positive for IgG. With electronic microscopy, they visualized hybrid myeloid cells with abundant endoplasmic reticulum and MPO-positive granules. The purified CD14^{+}myeloid cells also presented JH gene rearrangement, identical to the one found in the isolated myeloma cells. The in vitro culture systems provided evidence of the bi-lineal differentiation capacity of the myeloid cells. They suggest that aberrant expression of lineage-specific genes might be involved in the development of simultaneous hematologic neoplasia, like MM and AML (Akashi et al. 1991). However, most evidence shows no clonal relationship. Simultaneous leukemic clones probably arise from the interplay of genetics and a disturbed microenvironment (Higgins and Shah 2020; Klimkowska et al. 2021).

The genomic heterogeneity of t-MN is a product of a) the cytotoxic agent employed for treatment of the prior neoplasm, b) the age of the patient and c) the presence of a clonal hematopoiesis before exposure to the cytotoxic agent (Higgins and Shah 2020). For instance, alkylating agents like Melphalan and cyclophosphamide are strongly associated to mutations in genes like TP53 and PPM1D, which are commonly mutated in t-MN. Nonetheless, evidence shows bone marrow cells accumulate mutations with time (Higgins and Shah 2020). TP53-mutated clones may be found ancestral to t-MN. The selective advantage this mutation poses to cells may be

Table 1 Revised case reports and case series

Year	Articles	Type	Focus	Patients	Sex	Age	Plasma Cell Dyscrasia	Ig	Alkylating agents	Vinca alkaloids	Others	Symptoms/ signs	Cytopenia	Monocytosis	Follow up
1966	Nordensson	monocytic	simultaneous	7/310			MM		CPM, MPN	VCR					
1969	Poulik	monocytic	simultaneous				gammopathy								
1974	Osserman	monomyelocytic	therapy-associated		M	45	MM		MPN		Rxtx, urethane	lysozyme nephropathy		no	deteriorated
1974	Osserman	monomyelocytic	therapy-associated		F	41	MM	IgG	MPN		hormonals	fever; lysozyme nephropathy		yes	deteriorated
1974	Osserman	monomyelocytic	therapy-associated		M	28	MM		CPM, MPN		hormonals	fever, lysozyme nephropathy		yes	deteriorated
1974	Marcovic	monocytic	therapy-associated		M	48	MM	IgGK	MPN			WL, back pain, fatigue, pallor, n/v	anemia	yes	died
1979	Bierbach	monocytic	therapy-associated	3/100			MM		MPN		Rxtx				
1982	Naparstek	monocytic	simultaneous		M	68	PCD, leukemic phase	IgGK	CPM, MPN	VCR	biodegradable 1,3-bis(chloroethyl)-1-nitrosourea	weakness, pallor, hepatosplenomegaly	bicytopenia	yes	died
1984	Raz	monoblastic	simultaneous		M	68	MM	IgGK	MPN			pallor, hepatosplenomegaly	bicitopenia	yes	died
1984	Raz	monoblastic	simultaneous		M	60	MM	IgA				pallor, hepatosplenomegaly	anemia	yes	deteriorated
1989	Abe	monocytic	therapy-associated				MM								
2002	Levinson	monocytic	simultaneous		M	83	SMM	IgGL				dysuria	anemia	yes	

Table 1 (continued)

Year	Articles	Type	Focus	Patients	Sex	Age	Plasma Cell Dyscrasia	Ig	Alkylating agents	Vinca alkaloids	Others	Symptoms/ signs	Cytopenia	Monocytosis	Follow up
2003	Luca	monocytic	simultane-ous		M	77	MM	IgGL				diapho-resis, WL, juandice, hip pain	anemia	yes	deteriorated
2014	Muruktla	monoblastic	simultaneous		F	66	MM	IgGK				fatigue, WL	anemia	yes	died
2015	Shi	monocytic	simultaneous		M	78	MM	IgML	CPM		Thal	n/a	n/a	n/a	relapsed

MM Multiple myeloma, *CPM* cyclophosphamide, Melphalan, *VCR* vincristine, *Rxtx* radiotherapy, *Thal* thalidomide, *WL* weight loss further enhanced by the PPM1D mutation generated by chemotherapy, which is found in 3.3% of t-MN associated to MM (Higgins and Shah 2020; Mouhieddine 2018; Wong et al. 2015). Our case did not present mutations in TP53.

The presence of clonal hematopoiesis (CH) becomes pivotal in the understanding of t-MN and MM. Studies have found that a fifth of patients with MM have CH at the time of ASHCT (Mouhieddine 2018; Maia et al. 2020). Clonal hematopoiesis of indeterminate potential (CHIP) is defined by clonal hematopoiesis with absence of hematopoietic dysplasia and absence of increased blast cells in the bone marrow. The requirements for CH include the demonstration of a somatic mutation with a variant allele frequency of between 2 and 10%. The most frequent mutations are those also found in MN: DNMT3A, TET2, ASXL1. In the same line, the most common hematologic neoplasia associated with CH are myeloid neoplasms. Though it increases in prevalence with age, the absolute risk of developing a hematologic neoplasia is low (Heuser et al. 2016). External factors like radiation, chemotherapy, or environmental toxics might be factors that accelerate the progression from CHIP to dysplasia to leukemia.

A decent explanation to how both AML and MM may develop synchronous or metachronous to one another is the establishment of a permissive bone marrow microenvironment (Ghobrial et al. 2018; Li 2017; Kawano et al. 2013). Studies have shown mesenchymal stem and progenitor cells contribute to the survival and growth of myeloma cells and the maintenance of the myelodysplastic phenotype in MDS (Ghobrial et al. 2018; Li 2017; Calvi 2019). By secreting specific cytokines (including IL-6, VEGF, TGF-beta) stromal cells enhance the survival of both neoplastic populations and regulate the tumor immune response. Indeed, the immunosuppressive microenvironment set by the neoplastic cells may foster the development and/or progression of other hematological malignancies. In the setting of MM, antigen presentation and humoral response are ineffective. There is an increase in immunosuppressive cell types including Treg cells and myeloid-derived suppressor cells (Ghobrial et al. 2018; García-Ortiz et al. 2021; Zavidij et al. 2020). Gene expression studies have shown T cell populations have a more exhausted state (Ghobrial et al. 2018; Ryu et al. 2020). As for myeloid neoplasms, most data suggest genetic and epigenetic mechanisms are the main factors involved in their development. However, animal studies have shown homeostasis in the bone marrow microenvironment prevents the development of MNs (Li 2017; Calvi 2019).

Another consideration is that made by Osserman. The constant activation of immune cells due to chronic infections might help select clones with particular mutations. Infections in patients with MM is a common complication and it has been associated to relapse in disease, higher burden of PCs in bone marrow, presence of anemia, and neutropenia in the context of AHSCT (Brioli et al. 2019). The susceptibility to infections derives from an interplay among age, disease and therapy-associated factors that alter the immune response (Nucci and Anaissie 2009). Most of the infectious agents are bacteria, indicating a deficient innate immune response as well as a humoral immune response.

Immune dysregulation has become a constant component in MNs, specifically MDS. There is a pro-inflammatory environment in the MDS bone marrow: pathogen recognition receptors and pro-inflammatory cytokine receptors are over-expressed and DAMPs are constantly secreted. This pro-inflammatory environment leads to genotoxic stress, which may contribute to the genomic instability in MDS (Li 2017; Calvi 2019).

Monocytosis is uncommon in MM. Considering most t-MN are preceded by MDS, which is characterized by cytopenia, the finding of increased numbers of monocytes in peripheral blood might not only suggest the presence of a chronic infection but also of an incipient myeloid neoplasm.

According to the WHO classification of tumours of hematopoietic and lymphoid tissues, cases of t-MN present within 10 years of exposure to the therapy, have multilineage dysplasia, have no specific immunophenotype and present a complex karyotype, with abnormalities in chromosomes 5 or/and 7 and mutations in TP53 (Arber 2017). The immunophenotype coincides with the de novo counterparts, though blasts are usually CD34 positive and express myeloid antigens CD13 and CD33. To consider, thus, a monocytic leukaemia, more than 80% of the blasts in the bone marrow or peripheral blood are a combination of monoblasts, monocytes and monocytes. Their morphology is quite characteristic, with promonocytes and monocytes having convoluted nuclei and azurophilic granules in their cytoplasm. All three stages of maturation generate non-specific esterase reaction. Flow cytometry shows positivity for CD13, CD33, CD65, C15 and at least two markers of monocytic differentiation (CD14, CD4, CD11b, CD11c, CD64, CD68, CD36, and lysozyme) (Weir and Borowitz 2001; Peters and Ansari 2011). Immunohistochemistry shows positivity for lysozyme, CD68 and CD163. They have no specific genetic profile, except those presenting with erythrophagocytosis.

Without a TP53 mutation, the acute monocytic leukaemia our patient developed might be a de novo myeloid neoplasm. Establishing whether our case is a t-MN or not may not have a clinical impact but it confirms what studies have found in the pathophysiology of myeloid neoplasms: the bone marrow microenvironment plays a cardinal role in the homeostasis of precursor cells.

With the advent of new chemotherapeutics, multiple myeloma has become a chronic condition. Therapy-related myeloid neoplasms are therefore a newly found complication, with myelodysplastic syndrome and acute myeloid leukemias being the most prevalent. Monocytic phenotype is rarely encountered as a t-MN and infections must be thoroughly discarded. An integral diagnostic approach is key for diagnosing an acute monocytic leukemia in the context of therapy-related myeloid neoplasms. This must include phenotyping via flow cytometry, the morphologic characterization through biopsies and the genotyping of specific mutations.

Abbreviations
MM: Multiple myeloma; AHSCT: Autologous hematopoietic stem cell transplantation; VRd: Bortezomib, lenalidomide, dexamethasone; DRd: Daratumumab, lenalidomide, and dexamethasone; CTD: Cyclophosphamide, thalidomide and dexamethasone; t-MN/MN: Therapy-related myeloid neoplasm/ myeloid neoplasm; t-AML/AML: Therapy-related acute myeloid leukemia/ acute myeloid leukemia; t-MDS/MDS: Therapy-related myelodysplastic syndromes/ myelodysplastic syndromes t-MDS/MPN: Therapy-related myelodysplastic/myeloproliferative neoplasms; CBC: Complete blood count; BMA: Bone marrow aspirate; CH: Clonal hematopoiesis; CHIP: Clonal hematopoiesis of indeterminate potential.

Acknowledgements
Not applicable.

Authors' contributions
TECV, MJLT, LGMM and DMMO all contributed equally to the case and writing of the manuscript. BSH contributed with the results on genetic testing. The author(s) read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 13 February 2022 Accepted: 15 March 2022
Published online: 20 April 2022

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