Myeloid Sarcoma of the Nasopharynx Mimicking an Aggressive Lymphoma

Jacques Raphael · Alexander Valent · Colette Hanna · Nathalie Auger ·
Odile Casiraghi · Vincent Ribrag · Stephane De Botton · Veronique Saada

Received: 12 August 2013 / Accepted: 24 September 2013 / Published online: 8 October 2013
© Springer Science+Business Media New York 2013

Abstract

Background Myeloid sarcoma (MS) is a rare extra-medullary tumour of the myeloid lineage, which can be a difficult diagnosis to make.

Case presentation We report the case of a 73-year-old male with a right-sided nasopharyngeal mass revealed on CT scan and MRI.

Results An initial cytological and histological examination suggested a high-grade lymphoma. Nevertheless, the final diagnosis was a MS with an unusual involvement of the nasopharynx that was treated with a conventional induction leukemia therapy. Eight months later, the patient had persistent thrombocytopenia and a bone marrow aspiration showed the dysplasia of a high grade myelodysplastic syndrome and cytogenetics detected t(3;21). The patient was treated with a 5-Azacitidine (Vidaza) protocol until overt progression and disease evolution.

Conclusion In conclusion few cases of MS involving the nasopharynx have been reported. Its diagnosis is often difficult and should be considered especially when a high index of suspicion is present and the immunophenotype of the malignant haematological cells is not clearly in favour of a lymphoma.

Keywords Myeloid sarcoma · Nasopharynx · Immunophenotype · Myelodysplastic syndrome

Introduction

A myeloid sarcoma is a tumor consisting of myeloblasts with or without maturation occurring in an anatomic site other than the bone marrow or peripheral blood [1]. The diagnosis is often difficult, especially when the disease occurs without any hematological bone marrow abnormality, and is based on morphological and immunohistochemical findings. The incidence of MS is not clearly known because of frequent misdiagnoses, but is reported in about 3 % of patients with acute myeloid leukemia (AML) [2], the diagnosis of MS being established by necropsy in some patients [3]. MS may be observed at diagnosis or at the time of relapse [1, 4, 5].

Case Presentation

We report the case of a patient diagnosed with a MS and a very unusual clinical presentation. A 73 year-old Caucasian man with no previous history, presented with a right-sided nasopharyngeal mass. A CT scan and an MRI of the nasopharynx revealed a mucosal thickening of the left maxillary sinus and filling of some right posterior ethmoidal cells (Fig. 1). The PET-CT Scan depicted abnormal FDG uptake in the nasopharynx (SUV max 5.25) and the cervical lymph nodes (SUV max 4). The blood count revealed slight hyperleukocytosis ($11 \times 10^9/L$) with monocytosis (2.3 G/L) without any other abnormality. The monocytosis fluctuated between 0.5 and 1.4 G/L for several days with a peak at 2.3 G/L. At the same time the CRP level was elevated and ranged between 35 and 75 mg/L without any overt sign of infection or fever. A bone marrow aspiration showed a normal marrow without any significant abnormality including acute myeloid leukemia. No

J. Raphael (✉) · C. Hanna · V. Ribrag · S. De Botton
Clinical Haematology Department, Institut Gustave Roussy
(IGR), 114 rue Edouard Vaillant, 94805 Villejuif, France
e-mail: Raphaeljack13@hotmail.com

A. Valent · N. Auger · O. Casiraghi · V. Saada
Biology and Pathology Department, Institut Gustave Roussy
(IGR), Villejuif, France

Fig. 1 CT Scan axial slices of the nasopharynx. **a** Mucosal thickening of the left maxillary sinus. **b** Filling of some right posterior ethmoidal cells

signs of dysplasia were noted on the peripheral blood and bone marrow smears. Cytogenetic analysis on the bone marrow was normal. Cerebrospinal fluid was acellular. A biopsy of the nasopharynx was done with biopsy imprints (touch preparations) for cytological examination. The histological examination showed malignant infiltration of medium to large-sized cells with an irregular nucleus, suggesting a high-grade lymphoma (Fig. 2, top). Touch biopsy imprints stained with MGG (Fig. 2, low) revealed a majority of atypical cells exhibiting a lymphoid appearance with a high nucleocytoplasmic ratio, loosely condensed chromatin, inconspicuous nucleoli and an irregular nuclear profile. After careful analysis, very fine coarse cytoplasmic granules within the malignant cells as well as very rare images of cytophagia were observed. However, the malignant cells did not express lymphoid

markers (CD20, CD79a, CD23, CD3, CD5, CD4, CD8, CD57), but stained positively for myeloperoxidase and for CD15 (Fig. 2, low). Flow cytometry of a tumor cell suspension obtained after gentle disruption of the biopsy specimen revealed a medium-sized clustered population of low granularity, expressing markers of myeloid assignment: CD13+, CD33+, CD117+, with positivity for HLA-DR antigen and negativity for immaturity marker CD34 (Fig. 3). Fluorescence in situ hybridization (FISH) analysis of paraffin-embedded tumour slides did not identify either the t(8;21) translocation or MLL gene dissociation. The final diagnosis was a MS unusually involving the nasopharynx with no bone marrow disease.

The patient was treated with conventional induction AML therapy: a combination of Idarubicin (Zavedos) (12 mg/m² day 1 and 2) and Cytarabine (Cytosar) (200 mg/m² day 1–day 7) followed by only one course of consolidation with Idarubicin (Zavedos) 12 mg/m² day 1 and Cytarabine (Cytosar) 1 g/m²/12 h day 1–day 5 due to a severe neutropenia and thrombocytopenia (grade 3–4) that appeared following the induction. The clinical outcome was favourable, the PET-CT Scan showed no abnormal FDG uptake, the bone marrow and blood count were normal except for a megakaryocytic hypoplasia. Eight months later, a new marrow aspiration was done in front of a persistent thrombocytopenia (grade 1–2) that was monitored and treated symptomatically at first. The bone marrow showed an excess of blasts (12 %) with monocytic differentiation associated with signs of dysgranulopoiesis. Bone marrow cytogenetic analysis revealed a t(3,21) (q26;q22) translocation (*EVII* and *RUNX1* rearrangement demonstrated by FISH), that was not found on the initial bone marrow aspiration and tumour biopsy. A high-risk myelodysplastic syndrome was diagnosed and a 5-Azacitidine-treatment (Vidaza) regimen was started (75 mg/m² per day for 7 days every 28 days). After 4 cycles the patient had a cytological remission (medullar blasts less than 5 %) without cytogenetic remission. The cycles were pursued until September 2011 (22 cycles). In December 2011 another bone marrow examination evidenced an overt acute myeloblastic leukaemia with more than 30 % of blasts; the patient was enrolled in a phase I trial with the Etoposide derived drug (F14512). After 2 cycles there was no response with the persistence of peripheral blasts and thrombocytopenia; the treatment was stopped. The patient died from disease evolution later on.

Discussion

Myeloid sarcoma (MS) is a malignant extra-medullary tumor of myeloid immature cells that is rarely reported. It can occur de novo and is considered as the equivalent of a

Fig. 2 Top 1,2,3 nasopharynx biopsy (HES staining): monomorphic diffuse infiltrate of medium to high-sized cells exhibiting a lymphoid appearance. Low touch biopsy imprints of the nasopharyngeal biopsy.

a and b (MGG staining): majority of atypical cells with irregular shaped nucleus. c (alpha naphthol/pyronine staining): tumour cell positivity for the myeloperoxidase reaction

Fig. 3 Flow cytometry of a tumour cell suspension revealed a medium-sized clustered population of low granularity, expressing markers of myeloid assignment: CD13, CD33 and CD117 with positivity for HLA-DR antigen and negativity for immaturity marker CD34

diagnosis of acute myeloid leukemia or in association with other myeloid disorders (mostly AML, myeloproliferative diseases especially CML and MDS) in many anatomical sites [1, 6]. A review was recently published of 17 cases with a MS of the head and neck region, mostly involving

the oral cavity and none having a nasopharyngeal involvement [2]. The nasopharynx can be the site of a variety of neoplasms and hematolymphoid lesions such as nasopharyngeal carcinoma, N/K cell lymphoma, Castleman's disease and follicular dendritic cell sarcoma [7–9].

Few cases of MS in the nasopharynx were reported in the literature [6, 10]. The recognition of MS from these other lesions is of clinical importance. The appropriate therapy is often delayed because of a high misdiagnosis rate especially when the MS is poorly differentiated [11].

The morphology findings of myeloid sarcoma are myeloblasts with or without findings of promyelocytic or neutrophilic maturation [12]. When the initial MS site involves the lymphoid organs, a non-Hodgkin lymphoma is frequently initially suspected since lymphoma and MS may share morphologic similarities and expression of common leukocyte antigens like CD43 and CD45. The most reliable antigens reported in the literature that could be helpful for the diagnosis are:

- CD13 and CD68, markers of granular, monocytic and macrophagic cells
- Myeloperoxidase and CD117 markers for myeloid differentiation
- Lysozyme, a marker of monocytic lineage
- CD43 on the myeloid cells as well as the T cells and the B precursors [4, 11–14]
- CD34 and TdT expressed on immature cells

The correct diagnosis can usually be established by having a detailed history, examination of peripheral blood/bone marrow and immunohistochemical studies.

MS are more frequently observed with CBF (Core binding factor) AML: AML 2 with a t(8,21) translocation and usually a CD56-positive phenotype, and AML 4 with inversion of chromosome 16, or a translocation t(16,16) [7, 11, 15, 16]. Some cases of promyelocytic sarcoma with a t(15;17) have also been reported [17, 18]. In the present case, the patient developed a high-risk myelodysplasia eight months after the diagnosis of a MS of the nasopharynx. Cytogenetic studies demonstrated a t(3;21) translocation involving *EVII* (on chromosome 3) and *RUNX1* (on chromosome 21). Surprisingly, it was not detected at first neither on the nasopharyngeal tumour nor on the bone marrow analysis; either due to insufficient sensitivity of the FISH procedure or because of the secondary nature of the myelodysplasia. Indeed, hematologic malignancies associated with DNA-topoisomerase II targeted therapy are characterized by a relatively short latency period, and cytogenetic abnormalities in this setting involve mainly chromosome bands 11q23 (*MLL*) or 21 q22 (*RUNX1*) [19]. However, an eight months period of treatment, with lower dose than usual of anthracycline, because of a persistent thrombocytopenia, appears to be a very short latency and makes hardly probable the hypothesis of a treatment-related myelodysplasia.

No clear consensus or recommendation for the treatment exists in the literature. The prognosis seems more dismal than overt AML although it remains controversial [4, 15].

Patients who present with MS with no bone marrow involvement could have a better prognosis than those with systemic involvement [20]. Based on the recent published studies and/or reviews, combination chemotherapy used in AML (induction followed by consolidation) in association with a local resection seems appropriate [4, 15]. High-dose chemotherapy followed by stem cell transplantation may be associated with a higher probability of survival or cure [14]. Local radiotherapy may also yield better local tumor control if residual disease persists or the tumor relapsed after initial chemotherapy [21, 22].

In conclusion MS is a rarely identified disease when localized within the nasopharynx. A high index of suspicion is required for the diagnosis and MS should be considered in tumors of the nasopharynx especially those who are poorly differentiated and when the immunophenotype of the malignant hematological cells is not clearly in favor of a lymphoma.

Acknowledgments We would like to thank Lorna Saint-Ange for editing.

Conflict of interest The authors declare they have no conflict of interest/no financial disclosure to declare.

References

1. Campidelli C, Agostinelli C, Stitson R, et al. Myeloid sarcoma: extramedullary manifestation of myeloid disorders. *Am J Clin Pathol*. 2009;132:426–37.
2. Zhou J, Bell D, Medeiros LJ. Myeloid Sarcoma of the Head and Neck Region. *Arch Pathol Lab Med*. 2013 Mar 26.
3. Muss HB, Moloney WC. Chloroma and other myeloblastic tumors. *Blood*. 1973;42:721–8.
4. Paydas S, Zorludemir S, Ergin M. Granulocytic sarcoma: 32 cases and review of the literature. *Leuk Lymph*. 2006;47:2527–41.
5. Lee KH, Lee JH, Kim S, et al. High frequency of extramedullary relapse of acute leukaemia after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 2000;26:147–52.
6. Au WY, Kwong YL, Ho WK, et al. Primary granulocytic sarcoma of the nasopharynx. *Am J Hematol*. 2001;67:273–4.
7. Kwong YL, Chan AC, Liang RH. Natural killer cell lymphoma/leukemia: pathology and treatment. *Hematol Oncol*. 1997;15(2):71–9.
8. Tsai MH, Pai HH, Yen PT et al. Unusual localization of Castleman's disease: report of the first case in the nasopharynx. *Ear Nose Throat J*. 1997;76(10):731–5, 739.
9. Desai S, Deshpande R, Jambhekar N. Follicular dendritic cell tumor of the parapharyngeal region. *Head Neck*. 1999;21:164–7.
10. Sugimoto Y, Nishii K, Sakakura M, et al. Acute myeloid leukemia with t(8;21)(q22;q22) manifesting as granulocytic sarcomas in the rhinopharynx and external acoustic meatus at relapse after high-dose cytarabine: case report and review of the literature. *Hematol J*. 2004;5(1):84–9.
11. Menasce LP, Banerjee SS, Beckett E, et al. Extra-medullary myeloid tumor (granulocytic sarcoma) is often misdiagnosed: a study of 26 cases. *Histopathology*. 1999;34:391–8.
12. Roth MJ, Medeiros LJ, Elenitoba-Johnson K, et al. Extramedullary myeloid cell tumors. *Arch Pathol Lab Med*. 1995;119:790–7.

13. Alexiev BA, Wang W, Ning Y, et al. Myeloid sarcomas: a histologic immunohistochemical, and cytogenetic study. *Diagn Pathol*. 2007;2:42.
14. Pileri SA, Ascani S, Cox MC, et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia*. 2007;21:340–50.
15. Byrd JC, Edenfield WJ, Shields DJ, et al. Extramedullary myeloid cell tumors in acute nonlymphoblastic leukaemia: a clinical review. *J Clin Oncol*. 1995;13:1800–16.
16. Zhang XH, Zhang R, Li Y. Granulocytic sarcoma of abdomen in acute myeloid leukemia patient with inv(16) and t(6;17) abnormal chromosome: case report and review of literature. *Leuk Res*. 2010;34:958–61.
17. Tirado CA, Chen W, Valdez F, et al. Unusual presentation of myeloid sarcoma in a case of acute promyelocytic leukemia with a cryptic PML-RARA rearrangement involving multiple sites including the atrium. *Cancer Genet Cytogenet*. 2010;200:47–53.
18. Worch J, Ritter J, Fruhwald MC. Presentation of acute promyelocytic leukemia as granulocytic sarcoma. *Pediatr Blood Cancer*. 2008;50:657–60.
19. Kayser S, Döhner K, Krauter J, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. *Blood*. 2011;117:2137–45.
20. Tsimberidou AM, Kantarjian HM, Wen S, et al. Myeloid sarcoma is associated with superior event-free survival and overall survival compared with acute myeloid leukemia. *Cancer*. 2008;113(6):1370–8.
21. Chak LY, Sapozink MD, Cox RS. Extramedullary lesions in non-lymphocytic leukemia: results of radiation therapy. *Int J Radiat Oncol Biol Phys*. 1983;9:1173–6.
22. Bakst R, Wolden S, Yahalom J. Radiation therapy for chloroma (granulocytic sarcoma). *Int J Radiat Oncol Biol Phys*. 2012;82(5):1816–22.