

LETTERS TO THE EDITOR

Bradycardia during induction therapy with all-trans retinoic acid (ATRA)

Dear Editor,

Acute promyelocytic leukemia (APL) is a clinically and molecularly distinct subtype of acute myeloid leukemia that is distinguished by a recurrent chromosomal translocation, the t(15:17) translocation, which results in the fusion of the promyelocytic leukemia (*PML*) gene and the retinoic receptor α (*RAR α*) gene (*PML-RAR α*). The *PML-RAR α* fusion protein acts as an all-trans retinoic acid (ATRA)-dependent transcription factor and interferes with retinoic acid transcriptional regulation. This disruption can be overcome by superphysiologic concentrations of ATRA. Therefore ATRA is used to treat APL by causing the immature promyelocytes to differentiate to mature and functional myeloid cells [1]. The advent of ATRA has improved dramatically the outcome of patients in the last two decades [1,2], at a cost however of common drug-related toxicity.

A 64-year-old male patient with an unremarkable past medical history was admitted in our Hematology Department due to neutropenia and thrombocytopenia. The patient had a sudden onset of gingival hemorrhage in the last 24 hours. Because of the clinical picture, the morphology of blast cells in his blood smear and the clotting disorders the patient was immediately started on ATRA while peripheral blood samples were sent for molecular screening for *PML/RAR α* transcripts which proved positive. The patient was then diagnosed with acute APL and on the next day administration of ATRA in combination with idarubicin was initiated. One week after the onset of ATRA administration the patient developed asymptomatic sinus bradycardia. ATRA administration was not withheld and, despite that, bradycardia gradually resolved.

Sinus bradycardia may be due to sinoatrial node dysfunction, sick sinus syndrome or vasovagal responses. Transient sinus bradycardia commonly occurs during an acute myocardial infarction [3]. Increased intracranial pressure can also result in sinus bradycardia in a patient with neurologic dysfunction. Moreover, a number of drugs are responsible for sinus bradycardia. Other causes include hypothyroidism, hypothermia, severe prolonged hypoxia and certain infectious agents.

The patient's past and family medical history were unremarkable for cardiac disease and he was not on any kind of medication that concerned cardiac disease. Moreover, he went through a thorough cardiological assessment which revealed no intrinsic cause of his bradycar-

dia. Drugs with possible contribution to bradycardia were withdrawn. Neurological examination was normal as well as the rest of his daily clinical examination, with the exception of the persistent bradycardia. Finally, his laboratory evaluation did not reveal any specific abnormalities. We concluded that drug-induced bradycardia related to ATRA was plausible and applying Naranjo's algorithm we determined that the event was possibly due to ATRA.

ATRA has been reported to result in arrhythmia. However, and to our knowledge this is only the third documented case of ATRA-induced bradycardia, since two similar incidents of bradycardia during administration of ATRA have been reported so far [4,5]. Increasing awareness of such an uncommon adverse effect as bradycardia and close monitoring of patients are essential for recording and perhaps interpreting this disturbing, yet rarely dangerous event.

References

1. Huang M, Ye Y, Chen S et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. *Blood* 1988;72:567-572.
2. Wang ZY, Chen Z. Acute promyelocytic leukemia: From highly fatal to highly curable. *Blood* 2008;111:2505-2515.
3. Epstein AE, DiMarco JP, Ellenbogen KA et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;51:e1-62.
4. Maruhashi K, Wada H, Taniguchi M, Koizumi S. Sinus bradyarrhythmia during administration of all-trans retinoic acid in a patient with acute promyelocytic leukemia. *Rinsho Ketsueki* 1996;37:443-477 (in Japanese).
5. McGregor A, Hurst E, Lord S, Jones G. Bradycardia following retinoic acid differentiation syndrome in a patient with acute promyelocytic leukaemia. *BMJ Case Rep* 2012;2012.

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Successful treatment of myeloid sarcoma with local treatment modalities: The longest overall survival in published literature

Dear Editor,

Myeloid sarcoma (MS), briefly known as “Chloroma” or “Granulocytic sarcoma”, represents an extramedullary proliferation of immature myeloid cells or myeloblasts. It occurs mostly in adults aged 45–55 years and most commonly involves the skin, soft tissues, lymph nodes and bones [1,2]. Although it can precede the onset or occurs during the active phase of acute myeloid leukemia (AML), approximately one third of cases present as de novo disease without evidence of leukemia in blood or marrow and the so-called non-leukemic granulocytic sarcoma [3]. This subset of cases brings the greatest diagnostic challenge because MS can be easily confused with other hematologic malignancies [4]. AML emerges in the majority of patients within few months after diagnosis, so the prognosis is very poor [5]. We herein report a unique case of MS presenting as migratory skin and lymph node involvement without leukemic bone marrow infiltration during a 8-year follow up.

A 39-year-old man complaining of severe left groin pain for the past one year was referred to our oncology outpatient department in August 2006. On hip magnetic resonance imaging (MRI), destructive bone lesions that involved the left acetabulum and pubic bone compatible with primary bone lymphoma were shown. Biopsy was performed and immunohistochemical examination for LCA (CD45), CD3, CD79a, Tdt, CD99, CD1a and CD10 was done. It was strongly positive for LCA and all of rest were negative, suggestive of hematologic malignancy. Meanwhile, bone marrow aspiration and biopsy (BMAB) were done and found normocellular. Based on these results we accepted the patient as isolated bone lymphoma. The patient was administered i.v. cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) chemotherapy and pelvic radiotherapy. After 8 courses of chemotherapy and a total 3000 cGy, evident local regression was shown in the control hip MRIs which were performed every 6 months and the patient was in clinical remission.

Three years after uneventful clinical course, he manifested swelling located on the left lateral side trunk. On physical examination, there were several infiltrative granular purple pigmented nodules. Excisional biopsy from these lesions revealed monocytic monoblastic cell infiltration which was positive for LCA, CD43, CD68, myeloperoxidase (MPO) and lysozyme and negative for CD34, CD117, CD56, S100, CD1a and fascin, suggestive of acute leukemia. A repeat bone marrow biopsy was performed and showed no neoplastic infiltration. Upon these results, the patient received only local radiotherapy (3000 cGy) and the nodules disappeared. In February 2011, he presented with erythematous plaques on the right precordium.

Immunohistochemical studies from punch biopsy were positive for MPO, lysozyme, LCA, CD 68 and negative for TdT, mast cell triptase and toluidin blue, confirming the diagnosis of MS. Moreover, flow cytometry from peripheral blood revealed 42/uL CD34. Total leukocyte count was within normal limits. Neither blast cells in the peripheral blood nor infiltration in BMAB were identified. He was treated with 3000 cGy to the right chest wall with electrons (15 MeV) without chemotherapy. These plaques also disappeared with this treatment. Two years later, multiple swollen right axillary lymph nodes with the largest measuring 3.5 x 2.7 cm emerged in follow-up thorax CT. There was no radiologic evidence of solid organ metastases or other lymph node involvement. An excisional biopsy revealed diffuse cellular infiltration compatible with MS that effaced the nodal architecture, especially involving the interfollicular area and lots of neoplastic cells with irregular nuclei and high mitotic rate. These neoplastic cells showed strong immunoreactivity for MPO, lysozyme, LCA, CD68, CD43 and were negative for TdT, CD34, CD56 and CD123. MS with monocytic differentiation was diagnosed. Simultaneous complete blood count showed a hemoglobin level of 16.1 g/dL, 7900 / μ l leukocytes with 75.6% neutrophils, 7.9% lymphocytes and 223.000 / μ l platelets. Subsequent BMAB remained normal with <5% blasts. Based on these findings isolated migratory granulocytic sarcoma was diagnosed. In order to treat this condition 3000 cGy were delivered to the right axillary region after excision. Due to the patient's good performance status and without leukemic bone marrow infiltration no systemic chemotherapy was administered.

MS can develop at any anatomic site but skin and mucosa are the most common sites of involvement. The skin lesions generally occur on the trunk and present as multiple papules, plaques, or nodules of variable sizes [1,2]. Our patient suffered from granular purple pigmented nodules at the left lateral trunk and erythematous plaques on the right precordium on his clinical course. Both of these two lesions were positive for MPO, lysosyme, LCA and CD68. A cutaneous lesion on the precordium was negative for CD117 but it should be kept in mind that cutaneous MS are more commonly monocytic in origin and therefore are frequently negative for CD117 [1]. The prognosis of MS is generally poor, especially when associated with AML. There are few case reports about isolated MS which revealed that these patients have better outcome [2]. Because of its rarity, no definite therapy with and without accompanying malignancies exists [3]. Chemotherapy, local radiotherapy and surgical resection can be curative even in isolated forms and can prevent progression to leukemia [4]. Our patient was administered CHOP chemotherapy early in the course of disease and this might prevent

progress to leukemia, and radiotherapy given to various sites of MS lesions also resulted in localized remission. Ultimately, our patient never progressed to leukemic transformation as shown in the different BMABs and the peripheral blood showed no blasts during 8 years. This is the first MS report which has the longest overall survival in published literature and successfully treated with local and systemic treatment modalities.

References

1. Ritter JH, Goldstein NS, Argenyi Z et al. Granulocytic sarcoma: An immunohistologic comparison with peripheral T-cell lymphoma in paraffin sections. *J Cutan Pathol* 1994;21:207-216.
2. Vela-Chavez TA, Arrecillas-Zamora MD, Quintero-Cuadra LY et al. Granulocytic sarcoma of the breast without development of bone marrow involvement: A case report. *Diagn Pathol* 2009;4:2.

3. Pileri SA, Ascani S, Cox MC et al. Myeloid sarcoma: Clinicopathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia* 2007;21:340-350.
4. Menasce LP, Banerjee SS, Beckett E et al. Extra-medullary myeloid tumour (granulocytic sarcoma) is often misdiagnosed: A study of 26 cases. *Histopathology* 1999;34:391-398.
5. Yamauchi K, Yasuda M. Comparison in treatments of nonleukemic granulocytic sarcoma: Report of two cases and a review of 72 cases in the literature. *Cancer* 2002;94:1739-1746.

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Squamous cell carcinoma developed on Kyrle's disease scar

Dear Editor,

Squamous cell carcinoma (SCC) is the second common cancer of the skin, following basal cell carcinoma. It has a predilection for sun exposed areas of the body but it may also occur in areas of chronic scarring and ulceration.

Kyrle's disease (KD) is a chronic dermatosis of unknown etiology leading to skin ulceration and scarring. We herein present probably the first case of SCC developing on a KD chronic scar.

A 39-year-old male farmer was admitted to our department because of the development of an elevated and occasionally bleeding mass on the posterior surface of his left calf (Figure 1). The patient had a 6-year history of recurrent, histologically documented KD with typical skin lesion: yellowish-brown pruritic papules and nodules with a central keratin plug ending to scars and hyperpigmentation over the dorsum of both legs. He had been treated with antihistamines, emollients and topical medication: steroids, keratolytics, benzoyl peroxide and occasionally retinoids (tretinoin 0.05%, tazaroten 0.1%) and was also advised to avoid sun exposure, skin dryness and trauma.

He underwent a 4mm punch skin biopsy from the tumor and histological examination revealed the presence of a SCC. The lesion was surgically excised with healthy margins. The patient's further course was uneventful.

KD is a rare disorder except in the setting of chronic renal failure [1]. It has been classified to the acquired perforating disorders, clinically characterized by intense pruritus. The extensor skin surfaces of the extremities

are preferentially involved while mucous membranes are spared. Laboratory evaluation is essential for associated underlying disorders such as diabetes mellitus, hepatic abnormalities, congestive heart failure and renal disease [2]. However, idiopathic cases without any associated systemic diseases may occur, as in our case.

SCC may develop in areas of chronic scarring and ulceration such as burns, scars, vaccination sites, sinuses, stasis ulcers, chronic cutaneous lupus erythematosus, lupus vulgaris, epidermolysis bullosa dystrophica and necrosis lipoidica [3]. Tardio et al. reported a case of KD misdiagnosed as invasive squamous cell carcinoma [4]. According to the literature there are no reported cases of the development of a SCC on a KD scar.

In our patient, ultraviolet (UV) radiation may have played a pathogenetic role. Because of his occupation as a farmer, he had a history of significant sun exposure due to outdoors everyday activity. Additionally, his skin lesions were located on body surfaces prone to chronic trauma. We also assume that the prolonged use of topical steroids for his KD might have caused local immunosuppression which, in addition to chronic trauma and UV, could further promote the development of skin cancer on the affected areas.

In conclusion, clinicians should be alerted to closely examine and perform a biopsy in any clinical change, such as ulceration, bleeding, consistent inflammation, that may occur in a long-standing atrophic or hypertrophic scar of any origin. Early detection of cancer is essential for applying proper treatment modalities.

References

1. Hurwitz RM, Melton ME, Creech FT 3rd, Weiss J, Handt A. Perforating folliculitis in association with hemodialysis. *Am J Dermatopathol* 1982;4:101-108.
2. Harman M, Aytekin S, Akdeniz, Derici M. Kyrle's disease in diabetes mellitus and chronic renal failure. *J Eur Acad Dermatol Venereol* 1998;11:87-88.
3. Stavropoulos PG, Tebbe B, Tenorio S, Orfanos C. LE-associated squamous cell carcinoma. *Eur J Dermatol* 1996;6:48-50.
4. Tardio ML, Fasano D, Marucci G, Collina G. Hyperkeratosis follicularis et parafollicularis in cutem penetrans (Kyrle's disease). Description of a case. *Pathologica* 2000;92:195-197.

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Figure 1. Elevated mass on the posterior surface of the patient's left calf.

Are there new possibilities for the use of positron emission tomography in oncology?

Dear Editor,

Malignant diseases have a crucial role in overall morbidity and mortality all over the world. A great number of environmental carcinogenic factors leads to significant increase of morbidity and mortality in cancer patients. One of the diagnostic tools in oncology is positron emission tomography (PET) scan. Furthermore, PET is currently used in various clinical areas (cardiology, neurology, diagnosis and evaluation of inflammation and infection at different organ sites).

PET scan, in particular with fluorine-18-fluorodeoxyglucose (18F-FDG), has been already proven to offer considerable help in oncology [1,2].

Furthermore, there are some new radiopharmaceuticals which could be used in clinical investigation and in the therapy of malignant diseases [3,4].

Nowadays, the roles of PET in clinical practice include preoperative staging of cancers, differentiation between residual tumor and scarring, demonstration of suspected recurrences, monitoring response to therapy, prognosis and radiotherapy treatment planning.

In our opinion PET scan could have more important role in the therapy of malignant diseases.

First, some cytotoxic agents can be bound to radiopharmaceuticals (FDG or some others). Consequently, accumulation of these agents in malignant cells would lead to cell death. At the same time, due to the highly intensive metabolism of glucose in malignant cells, the concentration of these glucose-bound agents in normal cells would be below the level that could induce cell death.

On the other hand, the accumulation of radiopharmaceuticals in malignant cells could be used for subsequent application of some other agents which would be attract-

ed by radiopharmaceuticals in malignant cells, proven to cause cell death. It could even be cytotoxic lymphocytes labeled with that agent. Also, radiopharmaceuticals could be bound with a strong antigen, causing more intensive immunological response.

It would be very useful innovation to design a new device that could detect zones of radiopharmaceuticals' activity and to simultaneously treat these zones by radiotherapy.

We consider that these ideas could contribute in further investigations, the results of which could have significant clinical effects in the therapy of malignant diseases.

References

1. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. *Health Technol Assess* 2007;11:iii-iv, xi-267.
2. Li J, Xiao Y. Application of FDG-PET/CT in Radiation Oncology. *Front Oncol* 2013;3:80-86.
3. Deford-Watts LM, Mintz A, Kridel SJ. The Potential of 11C-acetate PET for Monitor the Fatty Acid Synthesis Pathway in Tumors. *Curr Pharm Biotechnol* 2013;14:300-312.
4. Huang C, McConathy J. Fluorine-18 Labeled Amino Acids for Oncologic Imaging with Positron Emission Tomography. *Curr Top Med Chem* 2013;13:871-891.

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