Unusual association of diseases/symptoms

Bradycardia following retinoic acid differentiation syndrome in a patient with acute promyelocytic leukaemia

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Summary

The authors describe a 28-year-old woman with newly diagnosed acute promyelocytic leukaemia (APL), who developed junctional bradycardia after receiving the molecular-targeted therapy all-trans retinoic acid (ATRA) and the anthracycline-based chemotherapeutic agent idarubicin following sepsis and the APL differentiation syndrome. The patient was asymptomatic of the bradycardia. Electrolytes and cardiac imaging were unremarkable. No other cases have been reported in this context and the mechanisms of the sinus node dysfunction are unclear. The patient achieved normal sinus rhythm after ATRA was withheld. The patient recovered and went on to achieve complete remission after re-starting ATRA and idarubicin.

BACKGROUND

Acute promyelocytic leukaemia (APL) is a subtype of acute myeloid leukaemia (AML). It is characterised by an accumulation of abnormal promyelocytes; resulting in pancytopenia. Clinical features include anaemia, infection, bruising and splenomegaly. Mortality is highest in the first week after diagnosis due to coagulopathy.¹ In 2008, 2343 cases of AML were diagnosed in the UK.² APL has been reported to comprise approximately 10% of all new AML diagnoses³ and occurs in both the adult and paediatric populations. APL is diagnosed using a full blood count, blood film, bone marrow aspirate, immunophenotyping and genetic studies. Morphologically the blast cells classically contain Auer rods and the nucleus may be bi-lobed.³

APL typically occurs because of an acquired balanced translocation between chromosomes 15 and 17, resulting in fusion of the promyelocytic leukaemia (PML) gene and the retinoic receptor- α (RAR α) gene.⁴ When the PML-RAR α gene complex is formed stem cell differentiation is blocked and proliferation of immature leukaemic cells occurs.⁴

The treatment of APL has been revolutionised by the use of all-trans retinoic acid (ATRA), which induces terminal differentiation of the abnormal promyelocytes by causing a structural change of the PML-RAR α gene. When ATRA is given with idarubicin chemotherapy a complete remission (CR) rate of 90%–95% is achieved.⁵ This is currently standard care for APL in the UK (the 'AIDA' regime). The suspected diagnosis of APL constitutes a haematological emergency and ATRA, along with blood product support, should be initiated even before confirmatory molecular analysis are available in order to mitigate potentially life-threatening coagulopathy.⁵

Treatment of APL with ATRA results in the APL differentiation syndrome in up to 50% of patients.³ APL differentiation syndrome is characterised by shortness of breath, hypoxia, fever, haemoptysis and pulmonary infiltrates on chest radiography.⁶ When APL differentiation syndrome

occurs, treatment with intravenous dexamethasone may help.⁷ The aetiology of the APL differentiation syndrome is not completely understood and various mechanisms have been proposed (table 1).³

CASE PRESENTATION

A 28-year-old woman presented with a 3 month history of weight loss, recurrent upper respiratory tract illnesses, visual disturbance and fever. She had no personal or family history of previous medical problems and she was taking no regular medication. On examination, she was feverish and there were bilateral retinal haemorrhages on fundoscopy.

Full blood count revealed pancytopenia (haemoglobin 2.8 g/dl, white cell count $9.8 \times 10^9/l$, neutrophils $0.4 \times 10^9/l$ and platelets $35 \times 10^9/l$). Blood film confirmed myeloid blasts; some with prominent Auer rods. Her C reactive protein was 162 and clotting profile revealed a raised prothrombin time and activated partial thromboplastin time with low Clauss fibrinogen. Bone marrow aspirate was consistent with APL and cytogenetics confirmed t(15:17). ECG and chest radiograph were normal on admission.

On day 1 ATRA was started at the standard dose of 45 mg/m²/day in two divided doses. In addition, allopurinol, as prophylaxis of tumour-lysis syndrome and the prophylactic antimicrobials aciclovir and itraconazole were commenced. Piperacillin 4 g/tazobactam 0.5 g were given to treat febrile neutropenia. She was also treated supportively with packed red cells, platelets, fresh frozen plasma

Table 1 Proposed mechanisms of APL differentiation syndrome³

- ▶ Malignant promyelocytes gain chemotactic properties when they differentiate due to ATRA, resulting in them infiltrating the lungs.
- ▶ Release of vasoactive cytokines from the differentiating cells resulting in capillary leak.
- ▶ Expression of adhesion molecules on myeloid cells.

APL, acute promyelocytic leukaemia; ATRA, all-trans retinoic acid.

and cryoprecipitate. Later that evening she had shortness of breath, haemoptysis and developed worsening fever. Oxygen saturations had dropped to 90% on room air and she had sinus tachycardia at 110 beats per min. A chest radiograph showed bilateral pulmonary infiltrates. Given the close temporal relationship with ATRA administration, a diagnosis of APL differentiation syndrome was favoured although, infection, pulmonary haemorrhage, fluid overload and transfusion-related lung injury were considered in the differential diagnosis. Intravenous dexamethasone was given and ATRA was discontinued. On day 2 idarubicin 12 mg/m² alternate days was commenced. By day 3 the symptoms of the APL differentiation syndrome had fully resolved and she was given half dose ATRA. On day 4 she received her second dose of idarubicin.

On day 5 the heart rate fell to 42 beats per min. There were no associated symptoms and the patient remained normotensive. ECG revealed junctional bradycardia with absent p waves (figure 1). Electrolytes, thyroid function and an echocardiogram were normal. Serial ECGs remained stable but unchanged. On days 6 and 8 she received her third and fourth dose of idarubicin respectively and on day 8 her ECG returned to normal sinus rhythm (figure 2).

OUTCOME AND FOLLOW-UP

ATRA and idarubicin are extremely important therapies in APL. As the risks of discontinuing the treatment were high, ATRA was re-instated at the standard dose. The patient remained on ATRA and idarubicin and achieved CR after her first cycle of treatment. She has now completed four cycles of chemotherapy with ATRA and has not suffered any further episodes of bradycardia.

DISCUSSION

In order for the myocardium to contract in an ordered fashion, the heart's electrical impulses are generated in the sinoatrial node (SAN) in the right atrium. The impulse is then directed towards the atrioventricular node (AVN) and subsequently down the Bundle of His to the Purkinje fibres.⁸ When the SAN is damaged, the AVN can pace the heart in lieu of the SAN, producing ECG abnormalities such

as absent p wave, inverted p wave or a p wave that appears within the QRS complex. The rate is usually between 45 and 60 bpm. Causes of this phenomenon include medications, inflammatory conditions, metabolic disorders or ischaemia.

On review of the literature there have been few reported cases of bradycardia in APL, associated with ATRA or idarubicin. One report described a case of sick sinus syndrome in a teenager with chronic myeloid leukaemia treated with idarubicin. However, this was not a direct relationship and the patient also received cytarabine⁹ which has been reported to cause bradycardia.¹⁰ Idarubicin is an anthracycline chemotherapeutic agent which is associated with cardiotoxicity. This is usually dose-related delayed cardiomyopathy but acute arrhythmias, mainly tachycardia, are also described. ATRA has been reported in association with an AVN block causing Stokes–Adams attacks in a gentleman with APL on day 25 of induction chemotherapy with ATRA, enocitabine and mitoxantrone.¹¹ ATRA was discontinued and normal sinus rhythm was restored 15 days later. The patient went on to receive consolidation chemotherapy without complications. It is not clear whether he received ATRA again. Another report documents sinus bradycardia in a 3 year old with APL 3 days after starting ATRA therapy.¹² The bradycardia was exacerbated when ATRA was taken, however did not recede when the patient stopped ATRA. The patient also received anthracyclines.

Leukaemic cells can infiltrate any body tissue, but clinically significant extra-medullary myeloid tumour has only rarely been associated with the heart.¹³ In a series of post-mortem examinations in patients with relapsed AML, microscopic blast infiltration of the myocardium was a frequent discovery,¹⁴ but the clinical significance of this finding is unclear.¹⁵ Heart block has been reported in AML which responded to radiotherapy¹⁶ and has also been reported in a patient with myelodysplasia with acute pericardial effusion in the context of likely transformation to AML; with myeloid infiltrate in the myocardium at postmortem.¹⁷ In addition, a patient with relapsed acute lymphoblastic leukaemia died from ventricular fibrillation due to prominent myocardial infiltrate on echocardiography.¹⁸

Figure 1 ECG showing junctional bradycardia.

Figure 2 ECG showing return to sinus rhythm.

The ultimate cause of the junctional bradycardia is unclear in our patient. The usual causes of sinus node dysfunction were excluded. There have been no reported cases of junctional bradycardia occurring secondary to her other medications. The cause is likely multi-factorial, with APL, ATRA, the APL differentiation syndrome, sepsis and the anthracycline therapy all potentially contributing to cause sinus node dysfunction. Although the APL differentiation syndrome had started to resolve it is possible that a similar infiltrative process which occurs in the lungs occurred in the myocardium. ATRA and idarubicin may also be responsible, although these drugs were continued without any further episodes. Echocardiography ruled out any gross clinically significant cardiac mass or pericardial effusion, which has been reported in most previous cases of symptomatic cardiac involvement of AML. It is possible that microscopic blast infiltration of the myocardium may have contributed. Cardiac MRI may have been of benefit to rule out other, more subtle, abnormalities.

This case reinforces regular monitoring of vital signs and low threshold for performing ECGs when bradycardias are suspected. It also demonstrates the importance of baseline ECGs in acutely unwell medical and haematology patients when receiving potentially cardiotoxic agents, especially when cardiac complications may occur later in the disease process. APL is a life threatening yet readily curable form of AML. This case highlights that potentially treatment-related adverse events can occur during induction therapy but that continuing with ATRA and chemotherapy is essential as long-term CR can be achieved as demonstrated in this case.

Learning points

- ▶ Admission ECGs are important.
- ▶ Close contact with cardiology.
- ▶ Monitoring of heart rate with APL during treatment with ATRA and idarubicin and low threshold for ECGs.
- ▶ Maintain treatment intensity with ATRA and chemotherapy.

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Competing interests None.

Patient consent Obtained.

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