Henoch–Scho¨nlein purpura (HSP) during treatment with anastrozole

introduction

The aromatase enzyme is responsible for oestrogen biosynthesis from androgens in postmenopausal women. Aromatase inhibitors (AIs) reduce oestrogen levels by decreasing aromatase activity and induce objective remissions in a significant proportion of postmenopausal women with advanced hormone-dependent breast cancer (BC) [1]. The third-generation AIs are currently considered the most effective first-line endocrine treatment of advanced endocrine-responsive BC since superior antitumour activity has been repeatedly demonstrated versus tamoxifen in large phase III
randomised trials in postmenopausal women [2–5]. Anastrozole is a third generation, reversible, nonsteroidal AI [6–7].

Henoch–Schönlein purpura (HSP) is an immunoglobulin A (IgA)-mediated, autoimmune, non-thrombocytopenic hypersensitivity vasculitis affecting mainly children and young adults. HSP is usually characterised by a triad of symptoms, including a purpuric rash beginning on the lower extremities and progressing to arms and trunk, abdominal pain or renal involvement and arthritis [8]. While the rash occurs in all cases, gastrointestinal, renal, joints, neurological and other organs' involvement may be present or not leading to complex and sometimes misleading differential diagnosis. The disorder represents a variety of leukocytoclastic angiitis of small vessels initiated by deposition of immune complexes [9]. Although the cause is unknown, HSP is often associated with infectious agents such as group A streptococci, mycoplasma, Epstein–Barr and Varicella Zoster viruses. It has also been associated with food reactions, cold exposure, insect bites, drugs and cancer [9–12]. Drug-associated HSP typically resolves rapidly after stopping the involved drug and reappears if medication is resumed [8]. Many cases are self-limiting in about 6 weeks and do not require specific therapeutic intervention. Nonsteroidal anti-inflammatory drugs can relieve joint and soft tissue discomfort; corticosteroids can be used to manage severe abdominal pain but are not recommended for treatment of rash, joint pain or renal disease alone as they do not affect the progression of the purpura. Cyclophosphamide, plasmapheresis, cyclosporine and azathioprine may be used in severe cases. The prognosis is usually favourable in the vast majority of patients except for about 5% of them who develop chronic renal insufficiency.

case report

A 67-year-old woman was diagnosed in 1999 with node-positive, hormone receptor- and c-erbB2-positive BC. Breast conserving surgery followed by radiotherapy was carried out and four cycles of adjuvant epirubicin plus cyclophosphamide were subsequently administered followed by 5 years of tamoxifen. In April 2005, she developed an ipsilateral supraclavicular relapse in association with an asymptomatic-isolated vertebral metastasis whereon anastrozole therapy was started: q3weekly trastuzumab and i.v. vinorelbine were subsequently added in May and September, respectively, due to progressive painful local disease. Radiotherapy (multiple fields, 2 Gy daily fraction, 54 Gy total dose delivered in 5.5 weeks) was carried out to the involved field and complete locoregional remission was achieved. No radiotherapy-related acute toxicity was observed.

Medical history included mild chronic renal insufficiency probably as a consequence of poststreptococcal glomerulonephritis in 1972, ischemic stroke in 2002 with mild residual sensomotor left hemisindrome, hypercholesterolemia, dyspepsia and reactive depression treated with cardioaspirin, atorvastatin, pantoprazol and paroxetin. Vinorelbine and trastuzumab were lastly given in November 2005 and the patient developed an upper airways infection at the beginning of December which resolved spontaneously after a few days without specific medication.

In January 2006, the patient experienced bilateral perigenicolar and perimalleolar painful oedema associated with transient single and confluent burning purpuric lesions arising on legs and subsequently extending to arms and trunk (Figure 1). She also complained of malaise without any abdominal pain: no clinical signs of gastrointestinal involvement or peripheral neuropathy were present. A clinical diagnosis of arthritis was made but antinuclear antibody, antineutrophil cytoplasmatic antibody, rheumatoid factor and cryoglobulin tests were all negative with no clinical picture of Sicca syndrome.

Blood tests did not show haematological and liver abnormalities and renal function, hematuria and proteinuria were stable during purpuric crisis. The patient refused a renal biopsy.

A skin biopsy from a right pretibial purpuric lesion showed leukocytoclastic vasculitis (Figure 2) and immunofluorescent staining demonstrated IgA deposits in the dermal vessels consistent with a diagnosis of HSP.

The literature review revealed a case of cutaneous vasculitis in a 78-year-old Japanese woman after 4 months of adjuvant treatment with anastrozole, which rapidly resolved after drug withdrawal [13].

Anastrozole, started about 10 months earlier, was at that time considered to be possibly related to HSP also in our patient: skin lesions and joint involvement resolved 2 weeks after drug interruption. Neither corticosteroids nor immunosuppressive drugs were given. Cardioaspirine, a possible alternative explanation for HSP [14], atorvastatin and paroxetin were maintained and pantoprazol, already used in the past without side effects, was stopped. Trastuzumab and vinorelbine were withdrawn for 2 months before the onset of the clinical picture and no association with cutaneous vasculitis has been described so far [15].

The recent upper airways infection could be correlated with the onset of HSP while a paraneoplastic aetiology was excluded in absence of clinical, biochemical and radiological signs of disease progression (thoracic/abdominal computed tomography and positron emission tomography scans).

Figure 1. Single and confluent purpuric lesions on both legs.
We report a case of HSP potentially related to short-term (10 months) treatment with anastrozole for advanced BC. Only one other case of HSP developed after short-term anastrozole treatment has been reported in the literature so far [13]: in both cases purpuric papules, skin ulceration and oedema disappeared within 2 weeks after drug withdrawal, without any additional treatment.

Other drugs with anti-estrogenic activity, such as tamoxifen, are known to induce vasculitis [16]. Interference between sex steroids levels and vasculitis was also postulated in a 22-year-old woman with intermittent HSP since puberty occurring typically during menstruation, who experienced prolonged remission during pregnancy and under contraceptive pills containing progesterone and oestradiol. Merryl et al. hypothesise an inflammatory mechanism involving neutrophil activation by excessive IgA modulated by exogenous and endogenous sex steroids [17]. Reduced oestradiol levels might be the trigger for IgA-mediated leukocytoclastic vasculitis in some patients. Third-generation AIs (anastrozole, letrozole, exemestane) are an important part of the modern therapeutic armamentarium for BC patients and are efficient in reducing circulating oestrogens to undetectable levels in postmenopausal women [1]. The increasing use of these compounds in the adjuvant and palliative setting might raise the incidence of rare side effects: cutaneous vasculitis could be one of these.

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references


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