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Case Report

Transient Cytopenias, Eosinophilic Hepatitis and Phenindione: The Dress Syndrome

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The "drug reaction with eosinophilia and systemic symptoms" (DRESS) syndrome encompasses the development of a severe rash, fever, abnormalities in blood counts and organ involvement within 2-6 weeks if initiation of a given drug and with persistence of the symptoms for a variable time after cessation of the offending medication [1]. Though Cacoub et al did not find oral anticoagulants amongst the agents linked to DRESS syndrome in their review [2] we would like to describe the occurrence of DRESS syndrome after phenindione intake in a 32 year old woman. She was admitted via casualty for fever (38.6C), a maculo-papular rash and generalised malaisethat started three weeks into treatment with phenindione. In December 2008 she had developed spontaneous axillary and subclavian vein thrombosis, treated initially with thrombolysis then with balloon dilatation: the latter revealed a stenosis at the thoracic outlet for which she underwent removal of the first rib. She received warfarin thromboprophylaxis for six months, discontinued in July 2009. Because of intermittent arm swelling though no clear development of post-thrombotic syndrome she was offered further thromboprophylaxiswith Fragmin (5000IU SC) from December 2010 to July 2011when warfarin was restarted but stopped in mid-January 2012 for alopecia. At this point she started phenindione.

Upon admission the patient had bilateral neck adenopathy (reactive hyperplasiaon lymphnode biopsy) and slight splenomegaly (14.2 cm by ultrasound). Liver enzymes were elevated as well as C-reactive protein (CRP). An extensive infectious disease workup was negative for hepatitis A, B, Cand E, cytomegalovirus, enterovirus, rotavirus,coxiella, bartonella, toxoplasma, leishmania and schystosoma; there was evidence of past contact for measles, parvovirus B19, rubella, HSV and Epstein Barr virus. Cultures of blood, urine, stool and throat were repetitively negative. Stools were negative for parasites. Anti-nuclear, anti-gliadin and alpha-1-antitrypsin were negative.A liver biopsy revealed acute hepatitis with a prevalent eosinophil infiltrate and fibrous expansion of the portal space. For several days since admission the patient had mild thrombocytopaenia and neutropaenia, followed by lymphocytosis, monocytosis and eosinophilia of two weeks duration. Having ruled out an infectious cause the patient was discharged home on Fragmin 5000IU SC and followed up in clinic. Her liver function tests and the CRP settled at the beginning of May 2012.

Apart from the rash and the fever, the DRESS syndrome includesinflammation and/or involvement of internal organs (liver 80%, kidney 40%, lung 33%, heart 15%, pancreas 5%) as well as lymphadenopathy[3]and blood abnormalities such as eosinophilia (52%), thrombocytopenia (25%) a typical lymphocytes (63%) with lymphopenia (45%) or lymphocytosis (25%) [1]. Our patient fulfilled all criteria with the addition of short lived neutropaenia and monocytosis coincidental with an acute phase reaction that prompted the infectious disease work-up. These features settled spontaneously after two weeks though the histology proven eosinophilic hepatitis resolved after 11 weeks. We are aware of one case of DRESS syndrome associated with the ingestion of warfarin ingestion [4] and we are describing the first case developing after phenindioneuse. Warfarin is a coumarin derivative belonging to the benzopyrone group of compounds whereas phenindione is an indandione compound: their chemical structure is quite different but they share keto groups susceptible of nucleophilic and electrophilic attack. The latter are partly responsible for an idiosyncratic drug reaction and partly an immune/allergic reaction[5]. Many drug reactions are accompanied by eosinophilia, suggesting an involvement of the Th2 immune response [6]. Warfarin intake has been associated with eosinophilia in peripheral blood [7,8] and pleural effusions [9,10] and phenprocoumon has been associated with eosinophilic hepatitis [11]. As novel cases accrue, future surveys may reveal that drug reactions with eosinophilia are at one end of the spectrum while DRESS syndrome is at the other end.

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