Superior Vena Cava Syndrome and Ovarian Hyperstimulation Syndrome

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For Editorial see page 501

Ovarian hyperstimulation syndrome is a rare complication of ovulation induction with exogenous gonadotropin administration. OHSS has a wide spectrum of clinical manifestations ranging from mild abdominal discomfort to potentially life-threatening events. OHSS causes ovarian enlargement, cyst formation and extravasation of fluids from blood vessels. A severe form of OHSS can cause hyperviscosity and, rarely, induce a hypercoagulable state with venous thrombosis. Here we present, to our knowledge, the most severe case of extracranial thrombosis in relation to OHSS: the complete obstruction of the superior vena cava.

OHSS = ovarian hyperstimulation syndrome

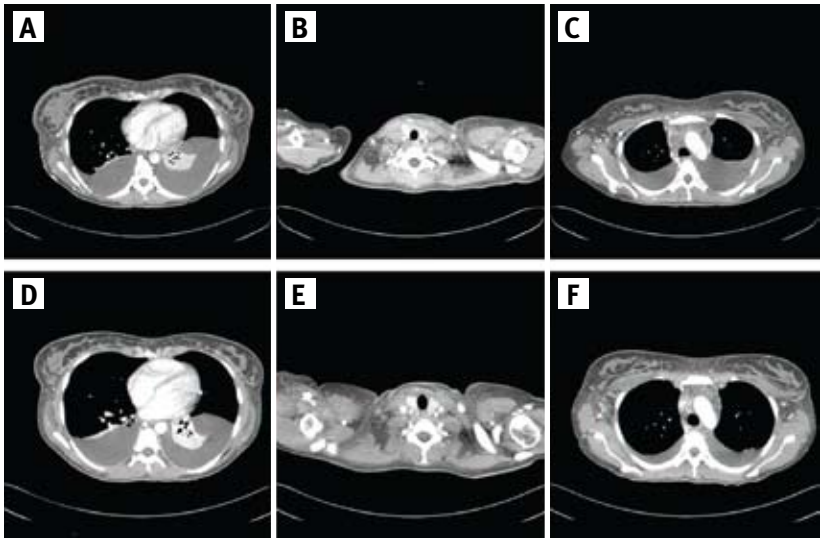
PATIENT DESCRIPTION

A 26 year old woman underwent fertilization treatments due to male factor and to polycystic ovarian syndrome. After an in vitro fertilization cycle, she developed severe OHSS (presenting with abdominal pain, large volume ascites and large ovaries) which required a long hospitalization. During her sixth week of gestation, she developed dyspnea, palpitations, severe weakness, and sharp pain in her right lower chest that intensified during deep inspiration. After admission to the emergency room the pain gradually subsided. She had tachycardia (120/min) with an oxygen saturation of 93% in room air. On physical examination, there were decreased breathing sounds and dull percussion on both lung fields, and an enhanced P2 heart sound over the pulmonic area was noted. Laboratory tests showed hyponatremia (125 mMol/L), leukocytosis (20,000/ml of which 85% were neutrophils) and thrombocytosis (596,000/ml). A chest X-ray revealed mild widening of the mediastinum and bilateral pleural effusion. Echocardiography demonstrated decreased filling of the left ventricle, a large pleural effusion and a small and hemodynamicaly insignificant pericardial effusion. Accordingly, a pulmonary embolism was suspected. Due to consideration for the fetus' safety and owing to the high index of suspicion, treatment with low molecular weight heparin was immediately initiated with a full dose of enoxaparin, 60 mg administered twice a day, without further evaluation (V/Q scan or angiography).

Three days later she developed neck edema, and maximal jugular venous congestion appeared, together with distension of the chest wall veins. Owing to a high level of suspicion of SVC syndrome she was rushed to the angiography laboratory where a scan revealed a complete

SVC = superior vena cava

CT images prior to heparin and tPA treatment **[A-C]** and after treatment **[D-F]**. **[A]** Bilateral pleural effusion and thoracic wall edema and congestion. **[B]** Bilateral jugular obstruction. **[C]** Complete obstruction of the superior vena cava. **[D]** Decreased thoracic wall edema. **[E]** Bilateral recanalization of the jugular veins. **[F]** Recanalization of the superior vena cava.



obstruction of the SVC along its entire length, and thrombi in the brachiocephalic and jugular veins. The azygos vein was open and congested. In addition, edema of the chest wall and bilateral pleural effusion were noted [Figure A-C]. The patient was transferred to the Intensive Coronary Care Unit for urgent thrombolytic treatment.

Treatment with tissue plasminogen activator was begun at a dose of 0.05 g/kg/hr with heparin supplementation. The following day there was no clinical improvement and fibrinogen levels had decreased to 870 g/day. The dose of tPA was doubled. The dosage of heparin was also increased gradually up to 35,000 units per day. Two days later the patient developed severe subcutaneous hematomas and hemoglobin levels dropped to 7.4 g/dl. Although the target fibrinogen level (150 mg/dl) was not yet reached, treatment was stopped. A computed tomography scan revealed significant thrombus canalization [Figure D-F]. The patient showed a dramatic improvement. Heparin treatment was continued until activated partial thromboplastin time was 62 seconds. The treatment was then replaced with enoxaparin adjusted according to factor Xa levels. Unfortunately, gynecological ultrasound at that time demonstrated a missed abortion. The patient was discharged in good general health, with oxygen saturation in room air of 95% though she still had mild exertion dyspnea, related to her pleural effusions. The effusions were gradually absorbed. Prior to her discharge the enoxaprin treatment was replaced by a standard coumadin regimen.

Several months after discharge the patient underwent a thorough workup to rule out a procoagulable state. All tests were negative except for a finding of activated protein C resistance heterozygosity. Serological workup for autoimmune and collagen disease was negative.

tPA = tissue plasminogen activator

COMMENT

In this report we described a severe complication of ovarian stimulation induction resulting in OHSS and SVC syndrome successfully treated with tPA in combination with heparin. OHSS is a rare complication of ovarian stimulation using gonadotropins. It occurs in 2%–6% of treatment cycles. Rarely, a severe form of OHSS may induce a hypercoagulable state with venous thrombosis. The most severe case of extracranial thrombosis in the literature so far was internal jugular thrombus with a free floating tip in the SVC [1]. Most reported cases of vascular thrombosis relating to OHSS have occurred in the upper extremities and neck. The rest were mainly intracranial and in the lower extremities [2]. Treatment with heparin was described in various protocols with reasonable success. However, chances of success appeared to be in inverse correlation to the magnitude of the thrombotic lesion; therefore, in more severe cases additional thrombolytic treatment might be required (2).

The etiology of vascular thrombosis associated with OHSS remains unclear. It seems that many of the severe cases had underlying predisposing factors such as polycystic ovarian syndrome (as in our case) or hereditary hypercoagulable states such as in factor V Leiden mutation [3]. The proposed mechanisms that may explain thrombosis are: hemoconcentration and hyper-estrogenism. Both mechanisms presumably relate to the extent of ovarian stimulation, i.e., ovarian size and number of follicles.

Hemoconcentration and activation of the coagulation cascade, a rise in thrombin-antithrombin III and plasmin-antiplasmin complexes, and increased platelet (as in our case) and tissue factor levels are seen in patients with OHSS. Tissue factor pathway inhibitor was reported to be significantly lower in OHSS patients [4].

The association between high estrogen levels and hypercoagulablity is widely documented. Non-physiological rises in estrogen levels during IVF and OHSS promote the expression of hemostatic markers. Studies of individual markers are confusing and do not reveal the qualitative effect of each marker on the overall coagulation process. It seems that the high level of estrogen correlates with increased clot stability and disturbances in the coagulation-fibrinolysis equilibrium [5].

Our patient is currently healthy. The question remains open if she will want to attempt another fertilization procedure in the future. OHSS seems to be a risk factor for thromboembolic events. In severe OHSS it is reasonable to consider low doses of low molecular weight heparin prophylactic treatment; the same applies to women with a history of thromboembolic events or known hereditary hypercoagulability.

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