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LETTER TO THE EDITOR

Chronic myeloid leukemia presenting late in pregnancy. Report of a case and a questionnaire reflecting diversity in management options

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Dear Editor,

During recent years, a fantastic progress in the treatment of chronic myeloid leukemia (CML) has been achieved with a number of novel, evidence-based options. However, there are still areas in the management of CML where clinical experience is limited and clear consensus is lacking. One such area is CML presenting during late pregnancy close to delivery.

We recently encountered a 38-week pregnant woman presenting with a CML in chronic phase, as described below. The situation prompted urgent therapeutic decisions. Although the management of the patient ended rather successfully, we observed a lacking concordance with regard to choice of therapeutic strategy among physicians at our unit.

Since this type of clinical scenario is relatively rare and seldom seen by the individual hematologist, there seem to be no unequivocally obvious steps to follow. We therefore wanted to seek expert opinions on CML presenting close to delivery. A questionnaire was sent to 25 renowned CML investigators in Europe, the US, and Australia with the case presentation and four accompanying questions. The results of this small survey are presented below.

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Case report (part 1)

A 42-year-old Caucasian woman was admitted to a local hospital in Stockholm after rupture of membranes 38 weeks into her second pregnancy. She had previously given birth to a healthy son. Her medical history included mild asthma. Her second pregnancy had so far been without complications, although a low hemoglobin level (nadir 77 g/l) had been recorded on several occasions. No determinations of white blood cell (WBC) or platelet counts had been performed previously during this pregnancy. On admission, the patient appeared well with no specific symptoms. Vaginal examination revealed the cervix dilated to ≤2 cm; no contractions and no palpable splenomegaly were noted. Body temperature was 38.0°C and CRP 77 mg/l. A full blood count revealed hemoglobin 98 g/l, platelet count 457×10^9/l, and WBC count 166×10^9/l with mature neutrophils 70%, eosinophils 2%, basophils 4%, metamyelocytes 8%, myelocytes 12%, promyelocytes 1%, and blasts 0.5%. Liver and kidney function tests were normal except for an increased lactate dehydrogenase (10.6 ukat/l; ULN 3.5). At 10 PM Friday evening, the attending gynecologist consulted a senior hematologist at Karolinska University Hospital. CML was suspected and later confirmed by bone marrow morphology, cytogenetics, FISH, and PCR.

The questionnaire included this first part of the case history with the following four questions:

Question 1. Would you prefer inducement of normal delivery or plan for a Cesarean?

Question 2. Would you start cyto-reductive treatment before delivery?

Question 3. What kind of cyto-reductive treatment would you choose?

Question 4. Would you consider low molecular weight heparin, or any other thrombosis prophylaxis, before delivery?

Fifteen (60%) of the experts responded to the questionnaire; ten from Europe, four from the US, and one from Australia. One expert gave a specific comment (see below).

In summary, three out of 15 experts (20%) would act in the same way as the patient eventually was handled. Thus, most responders (13/15; 87%) favored induction of a normal delivery (question 1). However, six of 15 (40%) felt that early institution of cyto-reductive treatment was necessary, which was not started in this patient (question 2). Among the six who would start cyto-reductive treatment, four would initiate hydroxyurea, one leukapheresis and hydroxyurea, and one leukapheresis only (question 3). In addition, thrombosis prophylaxis (low molecular weight heparin) was recommended by five of 15 (33%) experts with one favoring such prophylaxis after delivery (question 4).

The expert who responded in general terms to the four questions was of the view that it was impossible to answer the questions. According to this expert, the cooperation between an experienced obstetrician-gynecologist, neonatologist, hematologist, and someone with expertise in CML was required. It should be pointed out that the overriding question raised in the questionnaire was: 'How would you as a consulting hematologist care for the patient until a prompt delivery'? The attending hematologist of course had thorough discussions with both the obstetrician-gynecologist on second call and a coagulation expert on call.

Case report (part 2), with comments

The consulting hematologist regarded the patient not to suffer from any obvious CML disease-related symptoms and was of the opinion that her condition at that moment was not a medical emergency. Consequently, the decision to induce a normal delivery was taken since there were no apparent obstetric contraindications to such an approach. Since the patient suffered no symptoms related to leucostasis, leukapheresis was not performed and hydroxyurea was decided to be postponed until after delivery. However, pregnancy alone increases the risk of venous thromboembolism (VTE) by five times compared with non-pregnant controls [1]. Common risk factors for VTE include age over 35 years and operative delivery (especially emergency Caesarean section in labor) [2, 3]. Despite leukocytosis/thrombocytosis, patients with CML very rarely present with VTE [4] though thrombotic events were retrospectively recorded in 6% of chronic phase CML patients [5]. Pronounced leukocytosis in CML is associated with impaired microcirculation [6] but apparently not causing a high incidence of VTE with the exception of large number of blasts [7]. The patient had a moderate thrombocytosis and a marked leukocytosis. Trying to balance these risks, it was decided to give the patient a low dose of low molecular weight heparin (dalteparin 2,500 U) every 12 h. Seven hours after start of induction (oxytocin), the patient gave birth to a healthy daughter weighing 3,140 g. During delivery, there was a considerable blood loss (vaginal and perineal rupture) and the patient was given red cell transfusions. No platelet transfusion was given. After delivery, hydroxyurea treatment (1 g twice daily) was started and the patient declined to breast feed her baby in this situation. As stated above, the CML diagnosis was confirmed by bone marrow morphology, cytogenetics, FISH, and PCR. After 2 weeks of hydroxyurea, the WBC count was normalized (platelet count 882×10^9/l!) and the patient was invited to participate in an ongoing phase III comparing nilotinib versus imatinib. She started nilotinib at a dose of 400 mg bid.

In conclusion, this patient illustrates the varying clinical presentation of patients with myeloproliferative disorders. The diagnosis of CML would of course have been established earlier if the during pregnancy recorded low hemoglobin value had led to the determination of a full blood count. However, the patient responded well to oral iron supplementation and such tests were not performed until admittance to hospital. The results of the questionnaire also show the anticipated lack of total consensus among experts regarding the management of this patient. Notwithstanding this, a small majority favored a normal delivery and no cyto-reductive pre-delivery therapy. The thrombosis prophylaxis treatment given to the patient may have been redundant and only aggravated bleeding during delivery. However, in areas where evidence-based medicine does not fully reach out, this and many other clinical questions will remain unanswered. In these situations, however, decision making is still both important and certainly required.

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