Granulocytic sarcoma causing cord compression in a pregnant woman with acute myeloid leukemia and t(8;21)

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ABSTRACT

سرطان الخلايا الحبيبية (GSs) هو عبارة عن أورام صلبه ناشئة عن بشائر أو علامات نخاعية سابقة، وتحدث غالباً في حالات سرطان الدم النخاعي الحاد (AML)، الاضطراب النخاعي التشعبي، سوء النمو النخاعي، أو ما يسمى بالحثل الشوكي، ومن الممكن أن تصيب أية عضو من أعضاء الجسم، ولكنها على الأرجح تصيب العظام والخلايا اللينة في الرأس والعنق. والحقيقة إن سرطان الخلايا الحبيبية (GS) الناتج عن إنضغاط الحبل الشوكي يعتبر نادر الحدوث. كما تم اكتشاف وجود علاقة بين t-8;21 وبين سرطان الخلايا الحبيبية (GS). وعلى الرغم من حقيقة إن الـ t-8;21 يعتبر لدية فرصة شفاء طيبة، إلا أن المرضى المصابين بسرطان الخلايا الحبيبية (GS) وانضغاط الحبل الشوكي يتمتعون بفرص شفاء أقل من مرضى سرطان الدم النخاعي الحاد (AML) مع t-8;21. ويعتبر العلاج الإشعاعي، الكيماوي، والجراحي بأسلوب تحرير أو تخفيف الإنضغاط من الأساليب المقبولة علاجياً. ومع ذلك فإن أسلوب العلاج النشط مثل الزراعة ربما يكون مبرراً في مرحلة مبكرة في استراتيجية العلاج. والحمل لدى المصابات بسرطان الدم النخاعي الحاد (AML) أمر نادر الحدوث. وعلى حد علمنا، فقد تم تسجيل حالة حمل واحدة فقط لسيدة مصابة بسرطان الخلايا الحبيبية (GS) مع سرطان الدم النخاعي الحاد (AML). ونحن في هذا التقرير نسجل حالة سيدة حامل تم تشخيص حالتها بإصابتها بسرطان الدم النخاعي الحاد (AML / M2) مع t-8;21 خلال الثلاثة أشهر الأولى، والتي انتكست حالتها بالإصابة بسرطان الخلايا الحبيبية وإنضغاط الحبل الشوكي بالفقرات الصدرية في الفترة الأخيرة من الحمل. وضعت هذه السيدة طفلاً طبيعياً، وحدث لها سكون مرة أخرى بعد تلقيها العلاج الكيميائي. بعد مرور مدة قصيرة انتكست للمرة الثانية مع الإصابة بسرطان الخلايا الحبيبية (GS) وتوفيت بعد ذلك. ونحن نوصي بإعادة النظر في الاعتقاد بأن مرضى الـ (AML / M2) مع t-8;21 لديهم فرصة طيبة للشفاء. كما أنه يجب إعطاء اهتمام خاص مع أسلوب تطبيقي لعلاج سرطان الخلايا الحبيبية المصاحبة لـ (AML / M2) مع t-8;21 لدى أية مريض.

Chloroma or granulocytic sarcomas (GSs) are solid tumors originating from myeloid precursors. Most frequently they occur in acute myeloid leukemia (AML), myeloproliferative disorder, and myelodysplasia. It may involve any organ system, but mostly it affects the bone and soft tissue of the head and neck. Granulocytic sarcoma resulting in spinal cord compression is rare. The association between t(8;21), and GS has been reported. In spite of the fact that t(8;21) is considered to be associated with good prognosis, patients with GS and spinal cord compression had less favorable prognosis than other AML patients with t(8;21). Radiotherapy, chemotherapy, and surgical decompression are the accepted methods of therapy. However, aggressive therapy such as transplantation may be warranted early in the therapeutic strategy. Pregnancy associated with AML is rare. In our research, only one case of pregnancy with GS and AML has been previously reported. We are reporting a pregnant female diagnosed with AML/M2 with t(8;21) at the first trimester, who relapsed with GS, and cord compression at full term. She had a normal baby, and achieved second remission post-chemotherapy. Unfortunately, shortly after this she had a relapse, and died.

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Granulocytic sarcomas (GSs) are extra-medullary tumors of immature myeloid cells in patients with acute myeloid leukemia (AML).[1] Granulocytic sarcoma was first described in 1811 by Burns.[2] The term 'chloroma' was coined by King in 1853[2] due to the green appearance of the tumor. The true incidence of GS is not known, and the great majority of GS are diagnosed at autopsy.[3] The incidence of GS in AML is 3-5%, however, an incidence of 18-24% is seen in the cases with t(8:21), and 25% in cases with infant leukemia.[4] Tumor deposit can involve any organ system, however, spinal involvement has a poor outcome. Isolated chloroma resulting in spinal cord compression is rare, and only 15 cases have been reported according to our

literature review.[5] Cytogenetic abnormalities according to French-American-British (FAB) classification, and the response to treatment represents the most important prognostic factors in AML.[6] The balanced translocation between chromosomes 8 and 21 [t(8;21)(q22;q22)] is most frequently associated with AML FAB-M2 subtype, and usually predicts a good prognostic outcome.[6] The association between t(8; 21) (q22;q22) and GS has been described in several reports, particularly in adults, but more often in pediatric patients.[6] However, the prognostic significance of AML with t(8:22) in association with GS has not been clearly defined. The association of acute leukemia and pregnancy is uncommon. Its incidence is estimated to be 1 in 75,000 pregnancies.[7] One pregnant patient with AML in association with GS was reported in the Japanese literature.[8] We are reporting a case with GS, causing cord compression in a pregnant lady with AML/M2, t(8;21)as uncommon presentation in pregnancy, and due to the poor outcome in this case, we suggest that optimal therapy needs to be carefully defined in cases where AML with t(8;21). Special consideration for therapeutic modality should be given to GS associated with AML/M2 and t(8;21).

Case Report. The patient is a 30-year-old female. She is gravida 4 para 3+0 in the twelfth week of her pregnancy, and was diagnosed with AML. She presented to our Emergency Department late November 2005 with headache and blurred vision, and her systemic review was unremarkable. Physical examination was fairly normal, but she refused the funduscopy as she could not tolerate the light in her eyes. Laboratory investigations were consistent with AML. It was explained to her and her husband that further investigations are required to confirm the diagnosis of AML, as well as, an MRI would be required to investigate her severe headache. She chose to discharge herself against medical advice, and refused further investigations and management. She came back at the twentieth week of her pregnancy as a referral case of AML from another hospital for further evaluation. She was on Diamox according to the referral report for her papilledema. Her MRI from the referral hospital was normal. Her main complaint was persistent headache with blurring of vision and vomiting for a few weeks. On examination, she was afebrile and her physical examination was notable for absence of hepatosplenomegaly and petechiae. She was conscious, oriented, and her central nervous system (CNS) examination was normal. Funduscopy showed bilateral early signs of papilledema with retinal hemorrhages. As she was having doubling of vision, cerebrospinal fluid (CSF) examination was performed to rule out CNS infiltration, and it was found to be negative. Further investigations including bone marrow and cytogenetic analysis confirmed the diagnosis of AML, FAB (M2) with t(8;21). The white blood count (WBC) was $15.4x10^9$/L, hemoglobin (Hg) was 8.9 g/dl, and platelet count was $15x10^9$/L. She was persuaded to agree to chemotherapy after lengthy discussion, while pointing out to her the side effects to the fetus. She received doxorubicin for 3 days, and ara-C for 7 days as per our protocol. She tolerated the first cycle of chemotherapy, and assessment of the bone marrow confirmed the complete hematological and cytogenetic remission. The pregnancy was followed closely by the obstetrician and was reassured that the fetus was in good condition. The patient and her husband refused second cycle of chemotherapy, and she insisted on going home against medical advice. However, she came back in May 2006 through our Emergency Department at full term with paraplegia. The WBC was $5.6x10^9$/L, Hg was 12 g/dl, and platelet count was $226x10^9$/L. Peripheral blood

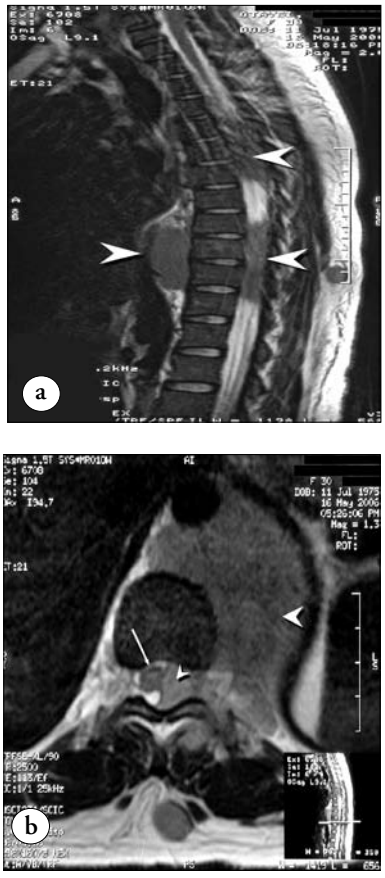

Figure 1 - **a**) sagittal T2-weighted MRI image shows segmental epidural hypointense soft tissue lesions at 2 levels (arrow heads) causing mass effect on the cord, and an anterior paraspinal soft tissue mass lesion (arrow head). **b**) axial T2-weighted MRI image shows a large left paraspinal soft tissue mass (large arrow head) that extends through the neural foramen (small arrow head), compressing and displacing the cord (long arrow).

film examination confirmed relapsed AML. Magnetic resonance imaging showed a large left paraspinal soft tissue mass compression of the spinal cord at T4/T5 and at T8/T9 (**Figure 1**). In consultation with the obstetrician, it was decided that immediate labor induction should be undertaken. She successfully delivered a normal baby boy. Our neurologist and neurosurgeon later assessed the patient, and both came to the conclusion that it was too late for surgical debulking. She was therefore placed on intravenous (IV) dexamethasone. Bone marrow examination confirmed the diagnosis of AML FAB (M2), and the cytogenetic analysis also confirmed the same t(8;21). Induction was started with chemotherapy, consisting of anthacycline, and ara-C. She achieved a second complete hematological and cytogenetic remission. She had 3 consolidation cycles of chemotherapy with high dose cytosine arabinoside, and adjuvant radiotherapy. she made a remarkable progress, however, she developed a persisting paraplegia. She was discharged home by the end of November 2006, to be followed up at our outpatient clinic. The last spinal MRI evaluation showed complete resolution of the epidural and paraspinal soft tissue mass lesions, and the cord is no longer compressed or displaced (**Figure 2**). She was seen again at the Emergency Department on the 26th of December 2006, in poor condition with fever and shortness of breath, and she was admitted to the intensive care unit. The laboratory investigations revealed a second relapse. The spinal MRI showed multiple extramedullary masses, and she was informed about the poor out come of the disease at this stage, and was referred for palliative care. However, she requested to be discharged home in order to be with her loved ones, where she later died.

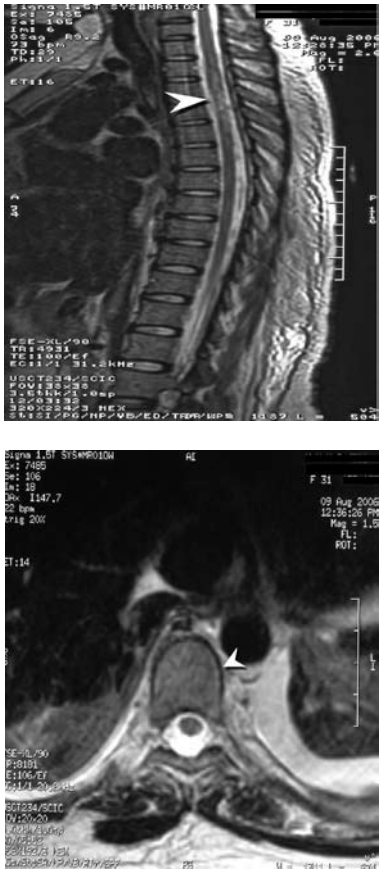

Figure 2 - T2-weighted MRI images showing complete resolution of the epidural (arrow head) and paraspinal soft tissue mass lesions, and the cord is no longer compressed or displaced.

Discussion. Granulocytic sarcoma is an extramedullary tumor of myeloid cells, and occurs in association with AML, myeloproliferative disorders (MPDs), or myelodysplastic syndrome (MDS), and is a well-known entity.[9] However, it may also occur without the full blown picture of acute leukemia.[5] The balanced translocation between chromosomes 8 and 21 is known to be associated with good response to chemotherapy and long leukemia free survival.[6] However, it is well known that t(8:22) is associated with GS, and the survival is less in those cases without GS.[6] On the other hand, management of AML coexistent with pregnancy is a serious clinical challenge. Virchow in his publication in 1845[7] reported that AML versus acute lymphoblastic leukemia is the most common type of acute leukemia seen during pregnancy, and the diagnosis was generally made during the second and third trimesters. This observation was confirmed in the Chelghoum study.[7] Chelghoum et al[7] reported 37 cases; 31 cases were with AML, and in 24 cases the pregnancies ranged between the second and third trimester. The favorable cytogenetic analysis were in 9 cases, and 4 of them were t(8:21). None of their cases presented or relapsed with GS. In our case, the diagnosis of AML with t(8:21) was made early in the second trimester. Paydas et al[4] reported 32 cases of GS with the ages ranging from 16-70 years. Granulocytic sarcoma was accompanied by AML in 13 cases, and was diagnosed simultaneously with leukemia in 5 cases, and preceded leukemia in 8. None of the 32 cases had GS involving the spinal cord. No cytogenetic tests were reported in any of the cases. However, the majority of AML cases classified were FAB M4, and none were FAB M2. None of the 32 patients was pregnant, like in our case. Granulocytic sarcomas infiltrating the extradural spinal area, and spinal cord invasion is rare.[5,10,11] Aizawa et al[11] reported a case of a 19-year-old male with an extradural GS at T5/6 to T7, as demonstrated by MRI. The patient recovered from the paraplegia that had progressed rapidly after excision of the tumor as an emergency operation. Both peripheral blood and bone

marrow examinations revealed AML. Tallman et al[10] reported 53 cases of AML at their institution between 1980 and 1992. Eight (15%) patients had t(8;21). Three of these 8 patients (38%) developed GS. Fujiwara et al[8] reported a case of a 35-year-old multiparous Japanese woman at 31 weeks of gestation, diagnosed as AML/FAB M2, and no cytogenetic analysis was reported. Her condition was complicated by GS in the cauda equina diagnosed by MRI. Our patient had a relapsed AML with GS causing cord compression diagnosed by MRI. Fujiwara et al[8] reported that their patient deteriorated rapidly. Cesarean section, laminectomy, and tumor resection were performed at 32 weeks of her gestation. The baby was female and weighed 1,774 g. Our case presented at term, and she had an immediate labor induction, and had successfully delivered a healthy baby boy. She was managed by IV dexamethasone followed by systemic chemotherapy, and she also had adjuvant radiotherapy. Chemotherapy treatment judged by the term of pregnancy, during the second or third trimester may not require termination of pregnancy,[7] as remission of AML and delivery of a normal infant are likely to be obtained. However, in the first trimester termination of pregnancy should be discussed,[7] due to the potential effect of chemotherapy causing fetal teratogenicity.

The outcome of AML with GS is well known to be associated with poor prognosis.[6] Tsimberidou et al[12] conducted a study to find out the survival in patients with nonleukemic GS. Twenty-one patients with nonleukemic GS, 1520 patients with AML (1.4% had GS), and 402 patients with high-risk myelodysplastic syndrome (1.1% had GS), all presenting to the MD Anderson Cancer Center between January 1990 and June 2002. Among the 20 patients with available cytogenetic analysis in tissue and/or bone marrow, 6 had chromosome 8 abnormalities. The median overall survival was 20 months (range: 1-75). The median survival of patients with chromosome 8 abnormalities was 12 months compared with 40 months in those without (p=0.17). We therefore suggested, that modified therapies for patients with chromosome 8 abnormalities were required.

Imatinib suppressed the c-kit activity and induced proliferation inhibition and apoptosis.[13] Expression of c-kit occurs in 81.3% of patients with t(8;21), more than in patients with other leukemias.[13] A recent publication by Wang et al[13] reported that Imatinib exerted a synergistic effect in apoptosis induction with cytarabine, thus providing a potential therapeutic for t(8;21) leukemia.

In conclusion, we suggest that the common belief of considering AML/M2 with t(8;21) as good prognosis needs to be revised. We also recommend CSF examination for this category of patients at presentation. Aggressive therapy such as transplantation may be warranted early in the therapeutic strategy. Introducing Imatinib to the protocol of AML in patients with abnormal chromosome t(8:21), might affect the outcome of the disease. However, more studies are still required in large centers with research facilities to determine these issues.

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