CASE REPORTS

UDC: 616.155.392-06:618.11-006
DOI: https://doi.org/10.2298/VSP210430062S

Leukemic infiltration of the ovary as an initial presentation of chronic myeloid leukemia in the chronic phase

Infiltracija jajnika kao inicijalna prezentacija hronične mijeloidne leukemije u hroničnoj fazi

Borivoj Sekulić*†, Ivanka Perčić*†, Marina Dragičević Jojkić*†, Marina Dokić*†, Milana Panjković†‡

University Clinical Center of Vojvodina, *Clinic of Hematology, ‡Department of Pathology and Histology, Novi Sad, Serbia; †University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

Abstract

Introduction. Extramedullary sites of leukemic proliferation, harboring an adverse outcome, are rare and usually found in the blastic phase of chronic myeloid leukemia. We report a case of a newly diagnosed patient with chronic myeloid leukemia in the chronic phase, with leukemic infiltration of the right ovary on disease presentation. **Case report.** The patient presented with abdominal pain, leukocytosis, and anemia. A peripheral blood smear indicated chronic myeloid leukemia, and cytoreductive treatment was started. Due to the worsening of the abdominal pain, computed tomography was done. It revealed a cystic tumor of the right ovary. The tumor was surgically removed. Bone marrow examination confirmed the diagnosis of chronic myeloid leukemia in the chronic phase. Immunohistochemical analysis of the ovarian tumor showed leukemic infiltration with 5% of blasts. The patient was treated with imatinib for one year. Due to treatment failure, imatinib was switched to nilotinib. Allogeneic stem cell transplantation was considered. **Conclusion.** This case highlights the critical role of the multidisciplinary team approach and close treatment monitoring to achieve the best possible outcome in these patients.

Key words:
drug therapy; leukemia, myelogenous, chronic, bcr-abl positive; neoplasm invasiveness; ovary.

Apstrakt

Uvod. Ekstramedularna proliferacije ćelija u hroničnoj mijeloidnoj leukemij je retka, najčešće se javlja u fazi blastne transformacije i znak je loše prognoze bolesti. Prikazujemo slučaj bolesnice sa leukemijskom infiltracijom desnog jajnika, kao inicijalnom prezentacijom hronične mijeloidne leukemije u hroničnoj fazi. **Prikaz bolesnika.** Bolesnica je hospitalizovana zbog bolova u trbuhu, leukocitoze i anemije. Pregledom razmaza periferne krvi posumnjano je na hroničnu mijeloidnu leukemiju i započeta je citoreduktivna terapija. Zbog pogoršanja abdominalnih bolova urađena je kompjuterizovana tomografija abdomena i male karlice. Ovom metodom je pokazano postojanje cističnog tumora desnog jajnika. Tumor je hirurški uklonjen. Pregledom kostne srži postavljena je dijagnoza hronične mijeloidne leukemije u hroničnoj fazi. Imunohistohemijskim pregledom tumora jajnika potvrđena je leukemijska infiltracija sa 5% blasta. Bolesnica je lečena imatinibom godinu dana. Usled nezadovoljavajućeg odgovora na terapiju imatinibom, lečenje je nastavljeno nilotinibom. Razmatra se alogena transplantacija. **Zaključak.** Multidisciplinarni pristup i praćenje terapijskog odgovora su neophodni za najbolji ishod lečenja ovih bolesnika.

Ključne reči:
lečenje lekovima; leukemija, mijeloidna, hronična, bcr-abl pozitivna; neoplazme, invazivnost; jajnik.

Introduction

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disorder characterized by a clonal proliferation of the hematopoietic stem cell. The proliferation is a consequence of the reciprocal translocation of chromosomes 9 and 22, which results in the formation of a shortened chromosome 22 called the Philadelphia (Ph) chromosome. As a result of the translocation, BCR and ABL genes get into close contact, and the product of their transcription is a highly active tyrosine kinase that causes the uncontrolled proliferation of myeloid cells. The disease has a

Correspondence to: Ivanka Perčić, University of Novi Sad, Faculty of Medicine, University Clinical Center of Vojvodina, Clinic of Hematology, Hajduk Veljkova 1-3, 21 000 Novi Sad, Serbia. E-mail: IVANKA.PERCIC@mf.uns.ac.rs

chronic, accelerated, and blastic phase. Most patients are diagnosed in the chronic phase (CP), characterized by hepatosplenomegaly, leukocytosis, and fatigue. Extramedullary sites of leukemic proliferation are rare and usually found in the blastic phase of the disease, harboring an adverse outcome [1].

Case report

A 24-year-old woman was referred to the doctor due to a sudden onset of abdominal pain and weakness. The pain was localized in the right lower quadrant. She had no significant previous medical history but reported that she lost around 5 kg over the last four months. Routine blood work showed leukocytosis and anemia. After a brief hospitalization in a regional hospital, she was transferred to a tertiary center. Upon admission to the Clinic of Hematology, the physical examination showed tenderness in the lower right quadrant and a palpable spleen 5 cm below the left costal margin. Her last period was fifteen days prior to admission.

Initial blood count showed an extreme leucocytosis with anemia and slight thrombocytosis [hemoglobin 69 g/L (reference range – RR: 120–160 g/L), white blood count 603 × 10^9/L (RR: 4–10 × 10^9/L), platelets 464 × 10^9/L (RR: 140–400 × 10^9/L]. A peripheral blood smear was indicative of CML in CP (blasts 0.01, promyelocytes 0.01, myelocytes 0.04, metamyelocytes 0.07, bands 0.07, neutrophils 0.69, eosinophils 0.01, basophils 0.04, lymphocytes 0.04, monocytes 0.02, nucleated red blood cells 2/100). Intravenous hydration with saline, low molecular weight heparin, and cytoreductive treatment with hydroxyurea was started. Further hematological diagnostics were postponed due to the worsening of the abdominal pain and the development of an acute abdomen on the second day of hospitalization. Computed tomography of the abdomen and pelvis revealed a large, partially cystic tumor of the right ovary 53 × 53 × 63 mm [anteroposterior (AP), laterolateral (LL), craniocaudal (CC), respectively] in close contact with the uterus and bladder, enlarged liver (AP 150 mm, CC 185 mm) and spleen (140 × 110 × 180 mm AP, LL, CC, respectively) (Figure 1). The patient underwent an emergency laparotomy. A ruptured cyst macroscopically resembling a cyst of corpus luteum and hematoperitoneum was found intraoperatively. The cyst was enucleated. The postoperative course was complicated with the development of a hematoma of the front abdominal wall and pelvis. For that matter, the patient underwent further three surgical drainages. After stabilization, a bone marrow tap and trephine biopsy were performed. The result was a hypercellular bone marrow with the predomination of mature granulocytes; the percentage of blasts was less than 5% in concordance with the diagnosis of CML-CP. Cytogenetics revealed the presence of the Ph chromosome (46, XX, t(9:22)(q34:q11)) in all 30 analyzed metaphases, and quantitative PCR showed 49% of the ratio BCR-ABL to ABL on the international scale. She was classified as low risk according to Sokal score (0.64), Hasford (513.6), EUTOS score (48 points), and EUTOS long-term survival (ELTS) score (1.0497). Pathohistological examination of the intraoperatively enucleated tumor showed infiltration of ovarian tissue with atypical myeloid cells in all states of differentiation (Figure 2). The number of $CD34^+/CD117^+$ blasts was around 5%. One month after surgery, treatment with imatinib was started. A hematologic response was achieved after 2 months. The patient did not reach a complete cytogenetic response after six months of imatinib treatment (Table 1). An optimal cytogenetic and molecular response according to European LeukemiaNet (ELN) guidelines was not reached even after one year of imatinib treatment (Table 1) [2]. Gynecological follow-up showed a normal finding. Due to treatment failure with imatinib, nilotinib 800 mg/day was introduced. Human leukocyte antigen (HLA) typification was performed only for the patient because she did not have siblings. We plan to repeat PCR and cytogenetics after six months of treatment with nilotinib and decide about allogeneic transplantation from unrelated matched donors.

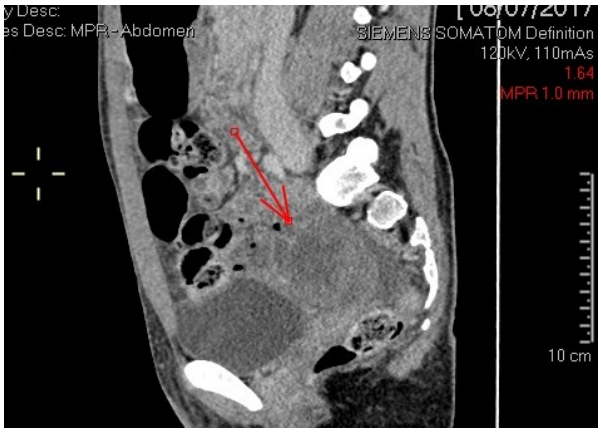

Fig. 1 – A sagittal computed tomography (CT) scan (abdomen and pelvis) showing a huge ovarian tumor (red arrow).

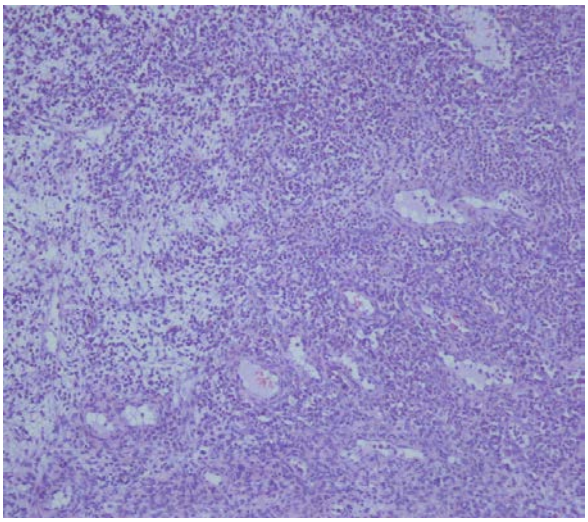

Fig. 2 – Histopathology of the excised ovarian tumor showing infiltration of myeloid cells in different stages of differentiation (hematoxylin and eosin staining, ×100).

Table 1

Results of treatment response monitoring

Duration of imatinib treatment	PCR (BCR-ABL to ABL)	Cytogenetics
Start	49%	46,XX, t(9:22)(q34:q11) / 30 metaphases
3 months	22%	Not done
6 months	1.5%	46,XX, t(9:22)(q34:q11) / 2 metaphases
1 year	0.69%	46,XX, t(9:22)(q34:q11) / 2 metaphases

PCR – polymerase chain reaction.

Discussion

Leukemic infiltration was previously described in CML, although the most common sites were lymph nodes, liver, spleen, and bones [1, 3]. Ovaries and other parts of the genital system are rarely affected by CML, especially in young females. The finding of leukemic infiltration in the ovarian mass was quite surprising in our patient. Mostly, complex cystic masses in young females are hemorrhagic cysts, endometriomas, a tubo-ovarian abscess, or ectopic pregnancy [4]. Solid masses can be benign or malignant ovarian tumors [4].

Pathohistological examination of the tumor is crucial for obtaining the correct diagnosis. Only morphological examination with hematoxylin and eosin stain can give an incorrect diagnosis [1]. Immunohistological positivity for myeloperoxidase, CD34, and CD117 was essential to determine cell origin and the number of blasts [1]. Fluorescent *in situ* hybridization (FISH) should be performed to prove the clonal origin of CML. In our case, it was not done due to technical difficulties.

In general, extramedullary leukemic infiltration indicates poor prognosis since it commonly represents an extramedullary blast crisis. Extramedullary blast crisis is most common in acute leukemia and the blastic phase of CML [1, 3]. Usually, it happens simultaneously or precedes marrow blast crisis by a few months [3]. It is very rare as an initial presentation of CML and in CML-CP [3]. Tyrosine kinase inhibotors (TKI) revolutionized the treatment and outcome of CML, inducing around 85% of major cytogenetic responses after 12 months of treatment with imatinib [5]. The response rate is even higher on treatment with nilotinib [6]. However, imatinib does not improve the prognosis of blast crisis dramatically [1]. Cytotoxic treatment followed by an early allogeneic stem cell transplantation is needed to induce remission in these patients [1].

In our opinion, our patient was not in an extramedullary blast crisis since the number of blasts in the infiltrated tissue was around 5%. That was very important for the treatment decision. Due to our country's regulations, imatinib was the only first-line treatment option. Nilotinib was introduced because of imatinib treatment failure after one year. We continued TKI treatment because the patient was still in CML-CP but decided to do HLA typification. The decision about the timing of allogeneic transplantation will be based on the results of PCR and cytogenetics after six months on nilotinib.

Another dilemma about CML and the ovarian localization of extramedullary hematopoiesis is fertility and childbirth. There is no solid evidence that TKI treatment impairs fertility, but medication should be stopped before pregnancy because of teratogenicity [7]. In the case of treatment with stem cell transplantation, fertility preservation methods should be used. Despite seldom reports of ovarian extramedullary tumors of CML origin, there is a possibility of gonadal infiltration by leukemic cells in hematologic malignancies. The critical question is the risk of disease relapse after in vitro fertilization. If the collected follicles carry leukemic residues, there might be a possibility of disease relapse during hormonal stimulation and the reimplantation of the follicles [8, 9]. Pregnancy itself could contribute to disease relapse [9]. One study on this topic showed that although leukemic cells were found in the ovarian tissue of patients with leukemia after complete remission, no leukemic relapse was detected after the tissue was transplanted into murine hosts [10].

Conclusion

Leukemic infiltration of the ovary is seldom found in patients with CML-CP, especially as an initial presentation. The finding or exclusion of extramedullary blast crisis is essential for decision-making concerning the treatment of these patients.

R E F E R E N C E S

1. *Levy RA, Mardones MA, Burch MM, Krause JR.* Myeloid sarcoma as the presenting symptom of chronic myelogeneousleukaemia blast crisis. Proc (Bayl Univ Med Cent) 2014; 27(3): 246–9.
2. *Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F,* et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020; 34: 966–84.
3. *Tsukamoto S, Ota S, Ohwada C, Takeda Y, Takeuchi M, Sakaida E,* et al. Extramedullary blast crisis of chronic myelogenous leukemia as an initial presentation. Leuk Res Rep 2013; 2(2): 67–9.
4. *Givens V, Mitchell GE, Harraway-Smith C, Reddy A, Maness DL.* Diagnosis and management of adnexal masses. Am Fam Physician 2009; 80(8): 815–20.
5. *O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F,* et al. IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003; 348(11): 994–1004.
6. *Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C,* et al. ENESTnd Investigators. Nilotinib versus imatinib for new-

ly diagnosed chronic myeloid leukemia. N Engl J Med 2010; 362(24): 2251–9.
7. *Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P.* Tyrosine kinase inhibitors and pregnancy. Mediterr J Hematol Infect Dis 2014; 6(1): e2014028.
8. *Abir R, Aviram A, Feinmesser M, Stein J, Yaniv I, Parnes D,* et al. Ovarian minimal residual disease in chronic myeloid leukaemia. Reprod Biomed Online 2014; 28(2): 255–60.
9. *Jadoul P, Kim SS.* ISFP Practice Committee. Fertility considerations in young women with hematological malignancies. J Assist Reprod Genet 2012; 29(6): 479–87.
10. *Greve T, Wielenga VT, Grauslund M, Sørensen N, Christiansen DB, Rosendahl M,* et al. Ovarian tissue cryopreserved for fertility preservation from patients with Ewing or other sarcomas appear to have no tumour cell contamination. Eur J Cancer 2013; 49(8): 1932–8.

Received on April 30, 2021
Accepted on May 26, 2021
Online First June 2021