Available online at: https://proceeding.researchsynergypress.com/index.php/cpmhs/index
RSF Conference Series: Medical and Health Science
e-ISSN *(to be processed)* / p-ISSN *(to be processed)*
Volume 1 Number 1 (2021): 14-24

Uterine Diffuse Large B Cell Lymphoma Non-Germinal Center Type with Multiple Organs Involvement: A Case Report

Yuktiana Kharisma[1,2], Afiati[1], Bethy S. Hernowo[1], Herry Yulianti[1]

[1] Department of Anatomical Pathology, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia
[2]Department of Anatomical Pathology, Faculty of Medicine, Universitas Islam Bandung, Indonesia

Abstract

Primary lymphoma of the uterine and cervix are a rare disease with nonspecific symptoms. Our aim was to present the unusual case and increase the awareness of uterine lymphoma, a rare and aggressive disease of the female genital tract which have a poor prognosis. Case presentation: A 52-year-old woman, complaining of continuous vaginal bleeding for two weeks. The patient was presumed to have uterine leiomyoma at the primary health care and given medication to reduce bleeding. Five months later, the patient had recurrent vaginal bleeding, then admitted to a private hospital in Bandung with indicating suspicion of cervical malignancy. Histopathological examination from the cervical biopsy showed Burkitt's lymphoma. On immunohistochemistry examination, the result supported Diffuse Large B Cell Lymphoma. Then, the patient was referred to Dr. Hasan Sadikin General Hospital Bandung for radiotherapy and chemotherapy management. The patient's general condition and vital signs were within normal limits. There were no intrapulmonary metastases, cardiomegaly without pulmonary engorgement on chest X-ray examination. Ultrasound examination concluded the suspicion of the isthmus and cervical malignancy without any pelvic lymphadenopathy. One month later, the patient had Magnetic Resonance Imaging (MRI) that showed multiple lobulated lesions in the isthmus and cervix, pressing on the surrounding organs with multiple lymphadenopathies. Abdomen CT-Scan revealed intrahepatic, L2-5 vertebral, and multiple lymphadenopathy involvement. In July 2021, the patient complained of severe shortness of breath. On the paracentesis fluid, we found the malignant lymphoma tumor cells. Unfortunately, two weeks after the examination, the patient died. Conclusions: We present a rare, aggressive, and poor prognosis disease of uterine diffuse large B cell lymphoma non-germinal center type with multiple organs involvement.

Keywords: *Diffuse Large B Cell Lymphoma; Uterine*

INTRODUCTION

Non-Hodgkin's Lymphoma (NHL) is a subcategory of lymphoma that occurs more often than Hodgkin's Lymphoma (HL) (Jaffe, Harris, Stein & Isaacson, 2008). According to the primary location, they are further subdivided into nodal and extranodal (Yang, Deisch, Tavares, Haixia, Cobb &Raza, 2017). As the name implies, lymphoma typically occurs within the lymphatic organs (nodal) and may have widespread systemic symptoms. NHL may affect the extranodal portion that includes the female genital tract, which is rare and accounts for 0.2 to 1.1% of all extranodal lymphomas in the female population (Singh, Madan, Benson & Rath, 2016). The ovary is the organ most often affected by primary or secondary female genital tract lymphomas followed by the uterus and the cervix, which are very rare. The diffuse

Corresponding author
Yuktiana Kharisma, yuktiana@gmail.com
DOI: *(to be processed)*

large B-cell lymphoma, follicular lymphoma, and Burkitt lymphoma are the main histological subtypes of non-Hodgkin's lymphoma (Nasioudis, Kampaktsis, Frey, Witkin & Holcomb, 2017). The most common histological subtype of female genital lymphomas is diffuse large B-cell lymphoma, which is difficult to diagnose. This is a rare case without typical clinical symptoms, which causes delays in early detection (Hilal, Hartmann, Dogan, Cetin, Krentel, Schiermeier, et al., 2016). A correct diagnosis can be achieved through immunohistochemistry studies (Binesh, Karimi, Vahedian & Rajabzadeh, 2012). The interdisciplinary cooperation between gynecologists, pathologists, is important to optimally manage patients. In addition, we present the case reports of uterine diffuse large B cell lymphoma with multiple organs involvement of a menopausal woman.

CASE PRESENTATION

A 52-year-old woman complained of continuous vaginal bleeding for two weeks. The patient went to primary health care and had been diagnosed with uterine leiomyoma and was given medication to reduce bleeding. After taking the drug for one month, vaginal bleeding gradually decreased and stopped. Five months later, the patient experienced recurrent vaginal bleeding and was referred to a private hospital in Bandung. The results of the examination revealed a suspicion of cervical malignancy. The patient has three children with a history of using hormonal contraception for the past 30 years. The patient also had a history of controlled hypertension and diabetes mellitus. The patient denied a smoking history. This patient then underwent a cervical biopsy procedure. A biopsy of 1x1x0.5 cm was taken and processed into histopathological preparation with hematoxylin-eosin staining. Microscopically, it consists of round, oval cells that grow solid, with polymorphic, hyperchromatic, and mitotic nuclei. A starry sky appearance has been seen (Figure 1). Therefore, the patient was diagnosed with Burkittt lymphoma on the cervix uteri.

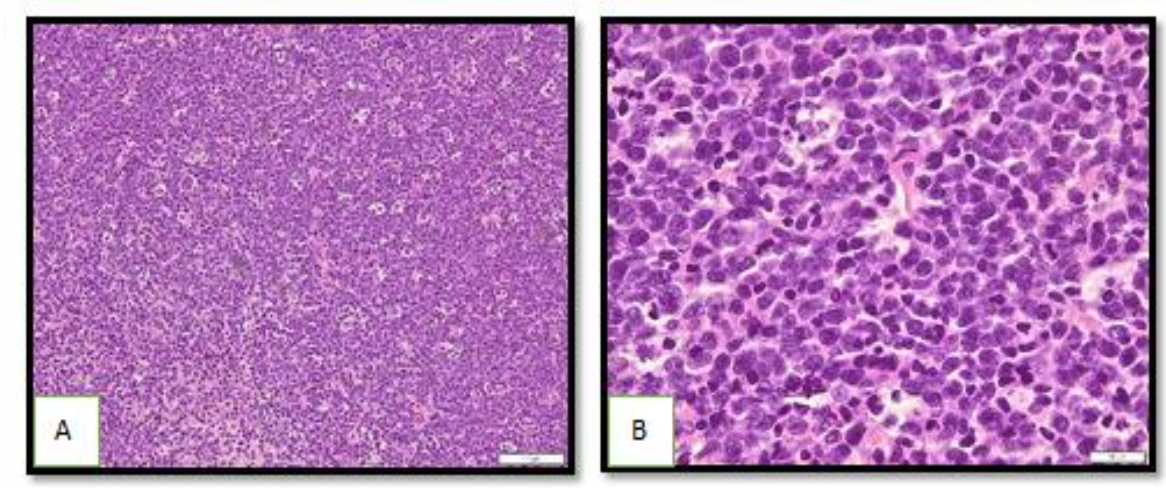

Figure 1. Histopathological appearance of a cervical biopsy. A. The tumor mass appears with a starry sky appearance (HE stains, 100x), B. Polymorphic, hyperchromatic cells, with robust mitosis (HE staining, 400x).

On immunohistochemistry examination, the results were positive on CD 20, and Ki67 was positive in > 50% of tumor cells, while immunohistochemistry staining of CD 10 showed a negative result. Those results support the Diffuse large B cell lymphoma Non-Germinal Center (Figure 2).

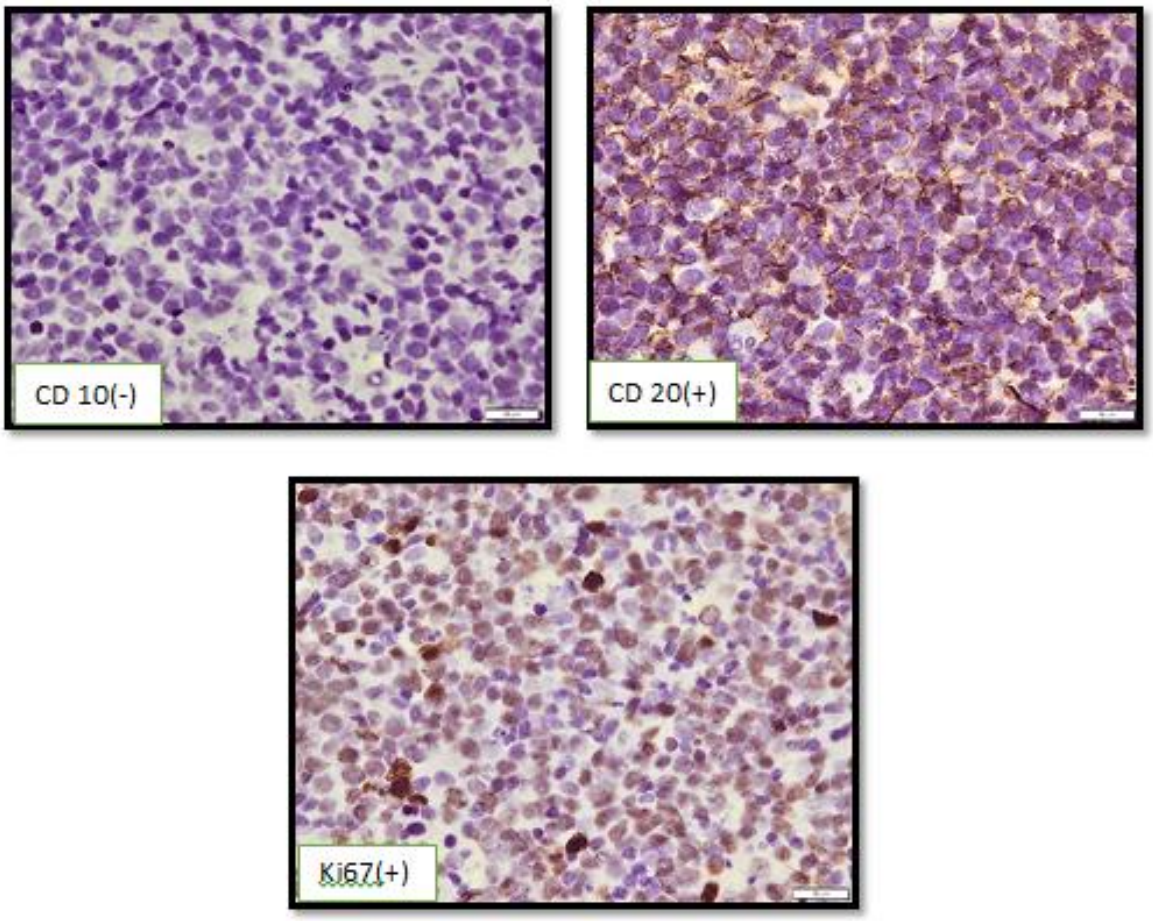

Figure 2. Immunohistochemistry staining of CD10 (-), CD20 (+), Ki67 (+) on cervical biopsy preparations. (HE stains; 400x).

In March 2021, the patient was referred to Dr. Hasan Sadikin General Hospital Bandung for radiotherapy management for as many as 35 cycles. On physical examination, the patient's general condition and vital signs were within normal limits. The first chest X-ray showed no intrapulmonary metastases, cardiomegaly without pulmonary occlusion (Figure 3).

ISSN *(to be processed)*

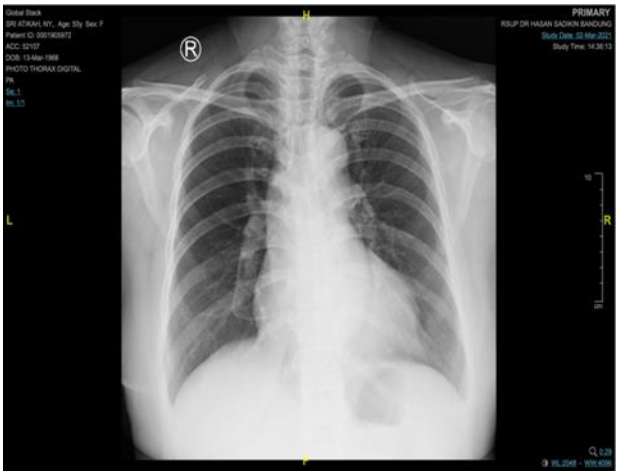

Figure 3. Radiological features of the thorax.

On the ultrasound examination (USG), it was found that the uterus was enlarged on size 4.84 x 7.68 x 10.99 cm. The mass was hypoechoic, lobulated, conglomerated, well-defined, regular margins at the isthmus up to the cervix sized 5.92 x 4.60 x 5.31 cm. On Color Doppler examination, it appears tortuous color flow intra-mass. The ovaries are difficult to visualize. Endometrial line: not thickened (0.23 cm), cul-de-sac: no visible collection of fluid. The pelvic lymph node scan result showed no hypoechoic lesions in the inguinal, hypogastric, obturator, parametrial, parailiac, and paraaortic regions. The urinary bladder is full, and the walls are not thickened, regular, does not appear hyperechoic shadow with acoustic shadow/mass. The right kidney is within the normal size, normal contour, normal parenchyma, and normal echo intensity. Parenchymal texture border with normal central echo complex. There is no hyperechoic shadow with acoustic shadow. The pelvic system is not dilated. The calice system is widened. The proximal ureter is not dilated. Left kidney normal size, normal contour, normal parenchyma, and normal echo intensity. Parenchymal texture border with normal central echo complex. There is no hyperechoic shadow with acoustic shadow. The pelvicalyceal system is dilated. Spleen, pancreas, gallbladder, liver, portal vein, and hepatic vein within normal limits. This ultrasound examination concluded that a lobulated inhomogeneous solid mass with tortuous color flow intramass in the isthmus and cervix was seen, suggesting cervical malignancy. No enlargement of the inguinal, hypogastric, hypogastric, parametrial, parailaccal, and paraaortic lymph nodes was seen. No intrahepatic metastases were seen. The liver, gallbladder, pancreas, spleen, bilateral kidneys, and urinary bladder were not presently abnormal (Figure 4). Then this patient was planned to undergo a pelvic MRI examination to detect extranodal involvement.

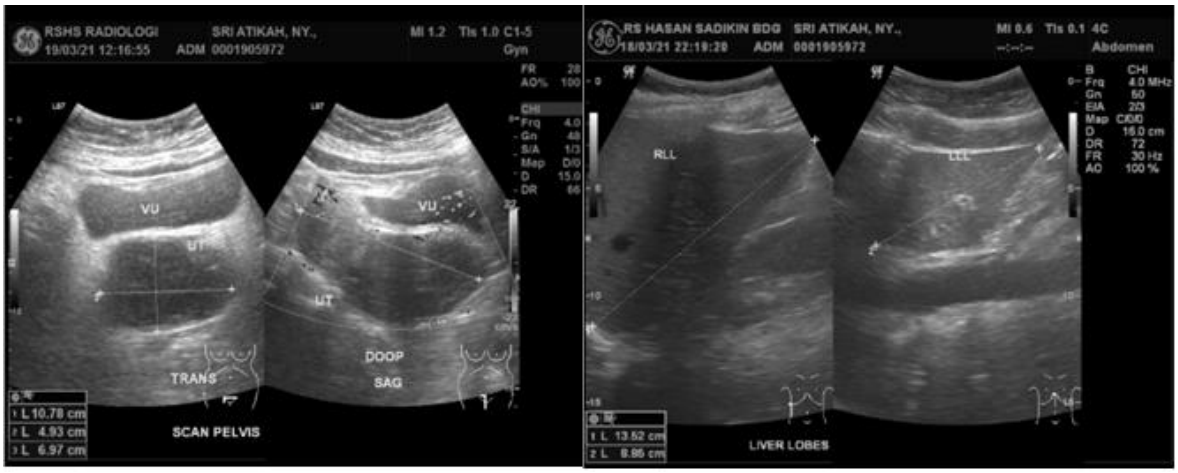

Figure 4. Ultrasonographic features of the abdomen.

Pelvic MRI examination with and without IV contrast and vaginal ultrasound gel was performed, with sequences T1WI and T2WI, T1WI+K+FS, T2 STIR axial-sagittal-coronal sections, and DWI-ADC axial sections. The uterus is globular asymmetrical in shape, enlarged in size (15.77 x 6.63 x 9.56cm), anteroflexed position. Endometrial line not thickened 0.53 cm (N < 1cm); Junctional zone not thickened. Multiple lobulated isointense lesions conglomerate in the fundus to the posterior cervix, measuring 7.19 x 8.06 x 10.62. The lesion gives a signal that is hypointense on T1WI and hyperintense on T2WI. The lesion is a restricted area on the DWI and ADC. Post-contrast appears to provide rim enhancement. The lesion appears to be pressing on the surrounding organs. Portio and parametrium are still intact, Cul-de-sac: no visible fluid collection in it (no void signal). Bilateral ovary: multiple cystic lesions with homogeneous density with firm boundaries with regular edges measuring 0.4 cm. The lesion gives a hyperintense signal on T1WI, hypointense on T2WI, and hyperintense on T2FS (Physiological follicular cyst). Post-contrast scanning does not provide enhancement. Bilateral fallopian tubes are not dilated. Endopelvic is within the normal limit. The urinary bladder is not fully filled, and the wall is not thickened. Paravesical space, rectum, normal perirectal fat, pelvic wall muscles and fascia, and peritoneum were still intact.

Post-contrast scanning showed no enhancement. In the pelvic and retroperitoneal lymph nodes, multiple hypointense lesions were seen, lobulated in the bilateral external iliac region, right internal iliac, and right inguinal on T1WI and T2WI post-contrast rim enhancement was seen. The conclusion of this MRI is that multiple lobulated isointense lesions conglomerate in the area of the fundus to the posterior cervix that compresses the surrounding organs (supporting Diffuse Large B. Cell Lymphoma); multiple lymphadenopathies in the external inguinal iliac region; and right internal iliac and inguinal.

ISSN *(to be processed)*

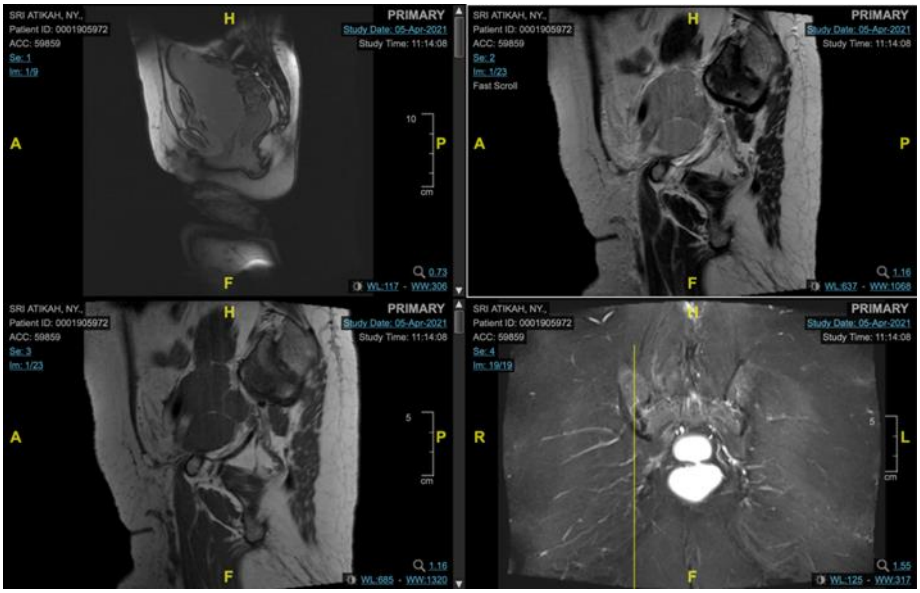

Figure 5. Magnetic resonance imaging.

The patient then underwent a CT-Scan of the abdomen with Contrast in June 2021. MSCT scan of the abdomen to the pelvis showed (Figure 6) a lobulated solid mass in the cervical region superiorly infiltrating the anterior body, posterior uterus, and fundus, anteriorly adhering to the posterior wall of the urinary bladder, posteriorly infiltrates the perirectal fat and adheres to the anterior wall of the rectum, which supports Diffuse Large B. Cell Lymphoma at the cervix.

Hepatosplenomegaly with a hypodense mass in segment III of the left lobe of the liver suggests intrahepatic metastases. Enlargement of the lymph nodes in the paraaortic, paraillia, right internal iliac, and left inguinal were seen. Pleural effusion with bilateral compressive atelectasis was seen. Osteolytic lesions of the L2-5 vertebral bodies suggest metastatic bone disease. Scanning of the gallbladder, pancreas, left kidney, and rectum showed no abnormalities.

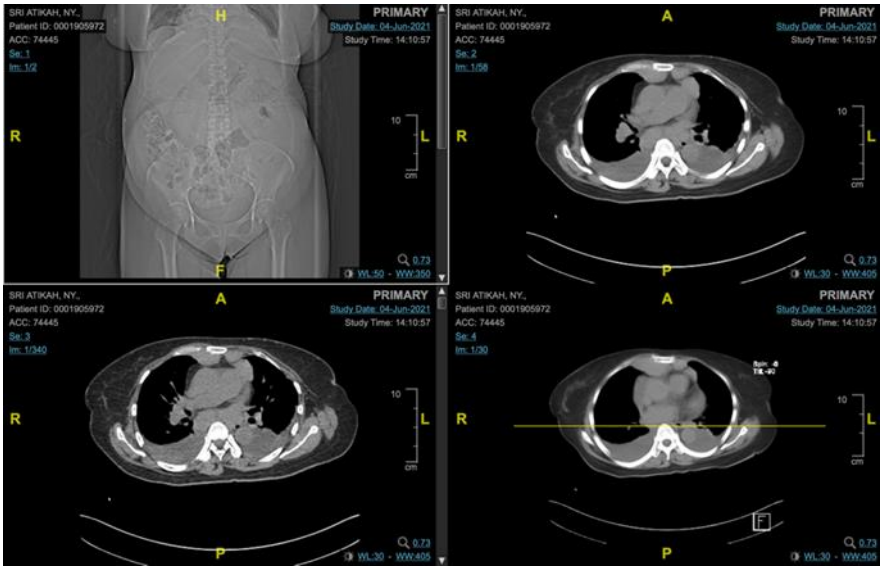

Figure 6. CT Scan abdomen

In July 2021, the patient returned for treatment to the Hasan Sadikin General Hospital Bandung with complaints of shortness of breath. Shortness of breath increases with activity and decreases when resting, sitting, and sleeping on the right side. There was no history of fever, cough, wheezing, and chest pain. On physical examination, the patient appeared moderately ill with compos mentis consciousness. The patient's vital signs were as follows: blood pressure 114/87 mmHg, heart rate 109x/minute, respiration rate 20x/minute, temperature 36.8C, O2 saturation 96% room air. anemic conjunctiva (+), icteric sclera (-), JVP 5+2cmH2O. On thoracic inspection, left chest movement was found. On percussion, the right hemithorax is dim. On auscultation, vesicular decreased in the right lung, rhonchi +/-, wheezing -/-. Normal S1S2 heart sound, murmur (-), gallop (-). On abdominal examination: bowel sounds + normal, soft flat, liver, and spleen not palpable. Warm acral extremities, edema -/-, CRT <3 sec.

Laboratory results were as follows: Hb 9.7 g/dL, Ht 29.5%, Leukocytes 4.730, Platelets 359,000, Erythrocytes 1.25 million/L, MCV 95.2, MCH 77.6, MCHC 81.5, Ureum 28.2 mg/dL, Creatinine 1.14 mg/dL, Na+ 129, K+ 3.5, Ca2+ 5.73, fasting blood sugar level 129 mg/dL, blood sugar level 2 hours post prandial 161mg/dL.

This patient underwent a chest X-ray examination, and the results showed a dilated mediastinum. The cast is difficult to assess; the right and left heart borders are covered with a shroud. Aortic calcification (-). Sinuses and diaphragm are covered in the sheath. In the lungs, the image of the right hilum is covered with a veil, and the left hilum is superpositioned with a cardiac shadow with a normal bronchovascular pattern. Lobulated opaque appearance in the paratracheal to perihiler bilateral. Impression of bilateral pleural effusions was seen, especially right with bilateral paratracheal to perihilar lymphadenopathy (Figure 7). Then this patient underwent right pleurocentesis to aspirate 600cc of pleural effusion fluid. On histopathological examination of the pleural effusion fluid, round and oval cells were found; scattered, with the pleomorphic nucleus, coarse chromatin, and scanty cytoplasm. There were also inflammatory cells of lymphocytes, PMN cells, histiocytes, and scattered mesothelial cells (Figure 8). The CD 20 showed immunoreactivity in pleural effusion smear. In conclusion, malignant tumor cells were found on the right pleural effusion fluid.

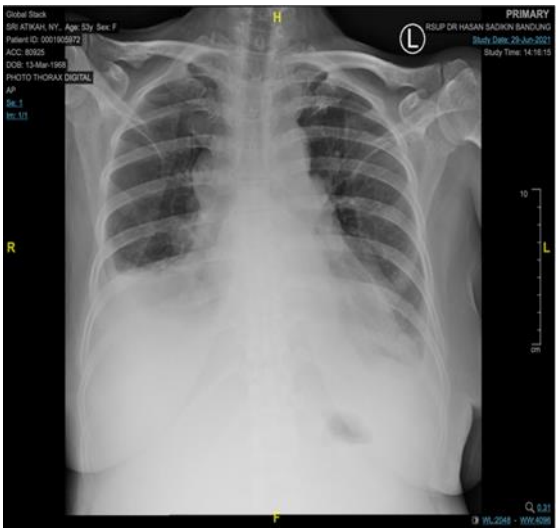

Figure 7. X-ray view of the chest.

ISSN *(to be processed)*

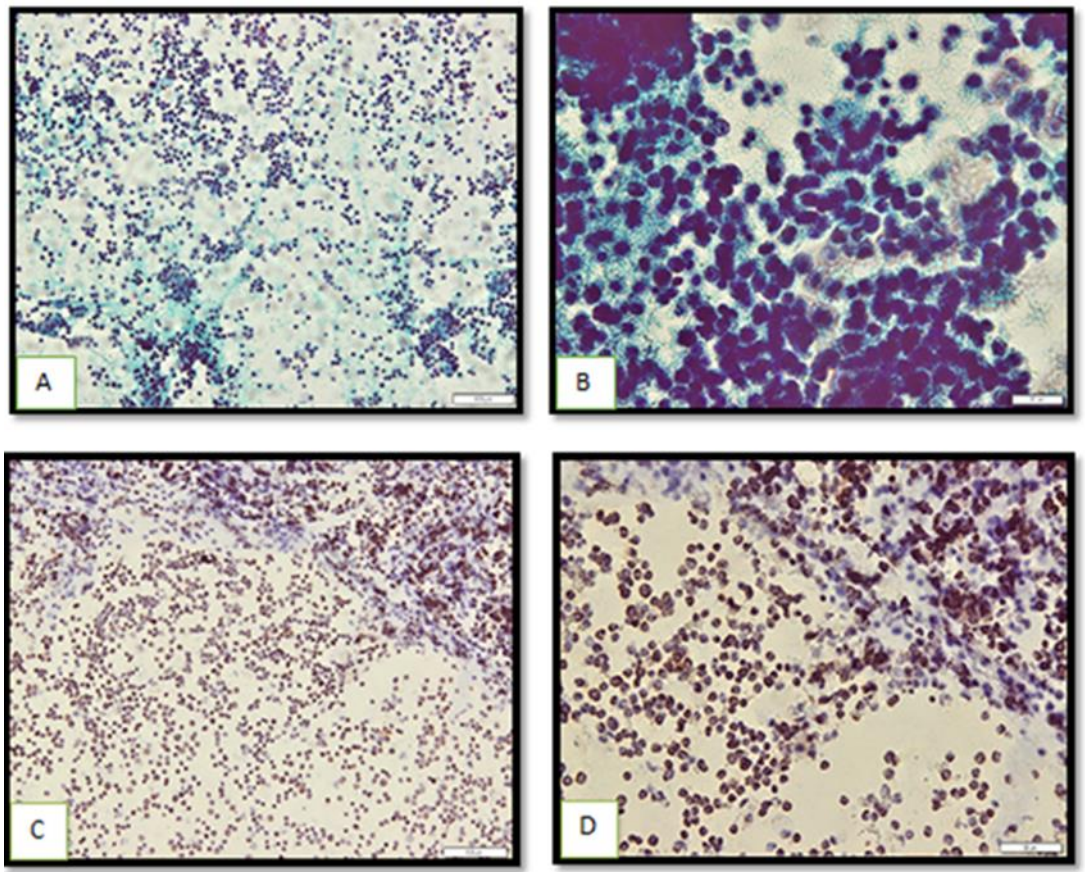

Figure 8. Histopathological appearance of a pleural effusion smear: Hematoxyllin Eosin stain (A.100x; B. 400x magnification); Immuno reactive of CD 20 (C.100x; D.200x magnification)

Therefore, the patient was clinically diagnosed with Diffuse large B cell lymphoma of the uterine cervix that disseminated to the posterior bladder wall, perirectal fat, and anterior rectum wall. Based on MRI and CT Scan examination, it was also found the involvement of the liver, L2-5 vertebral bodies, and paraaortic, parailiac, right internal iliac, left inguinal lymph node concomitant with pleural effusion and bilateral compressive atelectasis. On cytology examination, the malignant cell tumors were also found in pleural effusion smear. Two weeks later, the patient was reported dead.

FINDINGS AND DISCUSSION

The most frequently affected sites of primary lymphoma are the ovaries and cervix (Singh, Madan, Benson & Rath, 2016). The size and extension of the disease, age, number of nodes affected, LDH level, and lymphoma's grade are usually analyzed for the prognosis (Ferreira&Cunha, 2011).

Nevertheless, it depends on the histological subtype; for example, diffuse large B-cell lymphoma is more common between 35 and 45 years old, whereas follicular lymphoma is more frequent in people aged over 50; it happens in women during the fifth decade of life. According to the prior research, diffuse large B-cell lymphoma is more common in 35 - 45 years old women, compared to follicular lymphoma that common over the age of 50, Whereas Burkitt lymphoma affects five to ten years old (Pinto, Batista, Lourenço, Gonçalves, & Ramalho, 2014).

The rarity of this entity makes it difficult to diagnose (Pinto, Batista, Lourenço, Gonçalves, & Ramalho, 2014). There is no typical presentation of the symptoms, for example, abnormal uterine bleeding, pelvic pain, abdominal distension, and bloating (Clemente, Alessandrini, Rupolo, et al., 2016).

Since clinical evaluation and imaging studies cannot give a definitive diagnosis, most primary lymphoma of the female genital tract (PLFGT) is initially treated as a common gynecologic malignancy. The definitive diagnosis is obtained after surgery during the pathological examination of the surgical specimen (Singh, Madan, Benson & Rath, 2016). Immunohistochemistry examination plays a fundamental role in the characterization of the antibodies and in the classification of the subtypes of lymphomas (Yang, Deisch, Tavares, Haixia, Cobb &Raza, 2017).

In this case, the patient suffered from more than five months vaginal bleeding as a chief complaint. She underwent a cervical biopsy after being examined by the gynecologist that presumed cervical malignancy. The diagnosis of diffuse large B-cell lymphoma has been concluded after histopathology and immunohistochemistry evaluations.

Histopathology examination using Hematoxylin Eosin staining showed a picture of large and diffusely scattered tumor cells with pleomorphic, hyperchromatic, and mitotic cell nuclei. This appearance typically showed in the histopathological characteristics of lymphoma, which excludes other types of malignancy originating from epithelial and mesenchymal cell differentiation. In addition, there are many starry sky appearances that dominate the fields of view, which are usually typical in Burkitt Lymphoma. Nevertheless, this disease is most often found in children aged 5-10 years (Pinto, Batista, Lourenço, Gonçalves, & Ramalho, 2014). In this preparation, there is no typical follicular growth pattern typical for follicular lymphoma. From the results of the immunohistochemistry examination, the results obtained were positive CD 20, which indicated that the tumor cells were from the B lymphoma cell group. A high Ki67 >50% indicates a high degree of aggressiveness in this disease. CD 10 staining is not reactive (non-germinal center) associated with a poorer prognosis than diffuse large B cell lymphoma germinal center type (Mandato, Palermo, Falbo, Capodan-no, Capodanno, Gell, et al., 2014). A negative immunoreactivity of the Bcl 6 stain confirmed that the disease was not follicular lymphoma.

Examination of the chest cavity through X-Ray examination revealed normal results. No enlarged lymph nodes were found. On examination by ultrasound of the abdomen at the beginning of the period of illness, it was found that there was a mass in the isthmus and cervix, which was quite large in this patient, while the lymph nodes in the abdomen were within normal limits. From this examination, we cannot determine the primary location of this uterine tumor, whether it originates from the isthmus or cervix. According to Mandate et al., the diagnosis of primary lymphoma of the cervix can be made when there is no nodal involvement and no other site of extranodal involvement is established at the time of presentation type (Mandato, Palermo, Falbo, Capodan-no, Capodanno, Gell, et al., 2014).

The treatment of female genital tract lymphoma consists of a multimodal approach, including the gynecologist, the clinical oncologist, and the radiation oncologist, trying to individualize each treatment (Nasioudis, Kampaktsis, Frey, Witkin & Holcomb, 2017). This patient had a menopausal period, so fertility is no longer a treatment consideration. Patients come from rural areas which have minimal health facilities, and she did not get a complete examination at the hospital. About five months after the first vaginal bleeding, the patient was treated with radiotherapy. This patient underwent a series of radiotherapy for a total of 35 cycles. On MRI, lymphadenopathy in several pelvic areas after one month of therapy was found.

Gynecological involvement is seen in only 4% of female patients presenting diffuse large B cell lymphoma (Rush, Saltman, Prica, Breiner, Detsky, 2017), but when the female organs are involved, it is

ISSN *(to be processed)*

associated with a lower overall survival rate. The involvement of extranodal sites means the worst prognosis. The prognosis usually is analyzed based on the Ann Arbor staging system, size and extension of the disease, age, number of nodes affected LDH level, and lymphoma's grade. The Ann Arbor Staging System include: stage I, involvement of a single lymph node region (I) or lymphatic structure (Ie); stage II, involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or with limited, contiguous extra lymphatic tissue involvement (IIe); stage III, both sides of the diaphragm are involved (III) and may include spleen or local tissue involvement (IIIe); stage IV, multiple/disseminated involvement of one or more extra lymphatic organs, or isolated extra lymphatic organ involvement without adjacent regional lymph node involvement, but with the disease in distant site (s), or any involvement of the liver, bone marrow, pleura, or cerebrospinal fluid (i.e., bone marrow), which designates the absence (A), presence (B) of "B" symptoms. Stage IV (E) includes localized, solitary involvement of extra lymphatic tissue, excluding liver and bone marrow (Ferreira&Cunha, 2011).

At four months after the patient completed the radiotherapy session, she came back to the hospital with the chief complaint of shortness of breath. In this patient's pleural effusion, we found clusters of diffusely distributed round cells, some in clusters, which are characteristic of lymphoma. This was also confirmed by immunocytochemistry examination, which showed reactivity on CD 20 staining.

CONCLUSION

Diffuse large B cell lymphoma has been found in the uterine that disseminated to the posterior bladder wall, perirectal fat, and anterior rectum wall. Based on MRI and CT Scan examination, there are involvement of the liver, L2-5 vertebral bodies, and paraaortic, parailiac, right internal iliac, left inguinal lymph node concomitant with pleural effusion and bilateral compressive atelectasis. On cytology examination, the malignant cell tumors were also found in pleural effusion smear.

REFERENCES

A. Ferreira and T. M. Cunha. (2011) "Envolvimento do aparelho genital feminino por linfoma," Acta Radiológica Portuguesa, vol. 23, no. 91, pp. 25–32.

D. Nasioudis, P. N. Kampaktsis, M. Frey, S. S. Witkin, and K. Holcomb.(2017) "Primary lymphoma of the female genital tract: an analysis of 697 cases," Gynecologic Oncology, vol. 145, no. 2, pp. 305–309.

E. Pinto, S. Batista, C. Lourenço, J. Gonçalves, and G. Ramalho. (2014) "Gynecological lymphomas Linfomas ginecológicos," ActaObstetGinecol Port, vol. 8 , no. 2, pp. 201–205.

F. Binesh, M. Karimi zarchi, H. Vahedian, and Y. Rajabzadeh. (2012) "Primary malignant lymphoma of the uterine cervix," BMJ Case Reports, vol. 2012.

G. Yang, J. Deisch, M. Tavares, Q. Haixia, C. Cobb, and A. S. Raza. (2017) "Primary B-cell lymphoma of the uterine cervix: presentation in Pap-test slide and cervical biopsy," Diagnostic Cytopathology, vol. 45, no. 3, pp. 235–238.

Hilal Z, Hartmann F, Dogan A, Cetin C, Krentel H, Schiermeier S, et al. (2016) "Lymphoma of the Cervix: Case Report and Review of the Literature". Anticancer Res;36(9):4931-40.

Jaffe ES, Harris NL, Stein H, Isaacson PG. (2008) "Classification of lymphoid neoplasms: The mi croscope as a tool for disease discovery". Blood. ;112(12):4384-99.

L. Singh, R. Madan, R. Benson, and G. K. Rath. (2016) "Primary non-hodgkins lymphoma of uterine cervix: a case report of two patients," The Journal of Obstetrics and Gynecology of India, vol. 66, no. 2, pp. 125–127.

Mandato VD, Palermo R, Falbo A, Capodan-no I, Capodanno F, Gelli MC, et al. (2014) "Primary Diffuse Large B-Cell Lymphoma of the uterus: case report and review". Anticancer Res; 34(8):4377-90.

N. Clemente, L. Alessandrini, M. Rupolo et al. (2016) "Primary non-hodgkin's lymphoma of the vulva: a case report and literature review," Medicine, vol. 95, no. 10, Article ID e3041.

Rush R, Saltman A, Prica A, Breiner A, Detsky A. (2017) "Connecting the dots". NEJM 378: 1854.

Yang G, Deisch J, Tavares M, Haixia Q, Cobb C, Raza AS. (2017) "Primary B-cell lymphoma of the uterine cervix: Presentation in Pap-test slide and cervical biopsy". Diagn Cytopathol;45(3):235-38

ISSN *(to be processed)*