Case Report

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Mixed connective tissue and ovarian cancer: a case report

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Background: Mixed connective tissue disease (MCTD) is characterized by high titres of distinct antibodies: U1 ribonucleoprotein with variable clinical features seen in rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, and dermatomyositis. Limited case reports revealed the association between MCTD and cancer, like lymphoma, lung cancers, and others.

Case presentation: A 22-year-old female presented with enlargement of the abdomen and oedema of the lower extremities, gradually started 25 days The patient had been diagnosed to have rheumatoid arthritis. She was treated with 7.5 mg/week MTX for 6 months. Physical examination revealed: pallor, lower limb oedema, with synovitis and deformities of hands. The laboratory tests showed anaemia, elevated levels of creatine phosphokinase ESR, positivity of antinuclear antibody, anti-ds DNA, and antinuclear ribonucleoprotein. Urinary protein excretion was 1625 mg/24 h. Chest X-ray showed bilateral pleural effusion. Echocardiography revealed pericardial effusion Thoracic-abdominal and pelvic tomography showed a heterogeneous mass with a diameter of 5 × 6 cm at the expense of the right ovary. The mass was removed surgically, and a biopsy was taken, and was compatible with ovarian high-grade serous adenocarcinoma. A course of solumedrol 1 g/IV/3 days was applied, and then continue with 60 mg/day oral predlone. Later on discharge, she was taken 25 mg/day predlone, and methotrexate 10 mg.

Conclusions: Our case showed that the patient had no risk factors for developing ovary cancer. On the contrary, our patient was a young, non-smoker, without any previous treatment before the RA diagnosis was taken, and finally, she had 3 children with full-term pregnancy, and well health. This case highlights the importance of maintaining a high index of suspicion for malignancy in MCTD patients. However, further investigation on the role of the immune system in the development of ovarian cancer in women with autoimmune diseases including MCTD remains necessary.

Keywords: arthritis, lupus erythematous, systemic, MCTD, mixed connective tissue disease, ovarian neoplasms

Introduction

Mixed connective tissue disease (MCTD) is characterized by high titres of distinct antibodies: U1 ribonucleoprotein with variable clinical features seen in rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, and dermatomyositis[1].

MCTD occurs worldwide and in all races, with a peak incidence in adolescence and the 20 s. About 80% of people who have the disease are women[2]. The cause of MCTD is unknown, although several factors suggest that mixed connective tissue disease is a distinct disorder in its own right[2]. These include symptoms shared by several rheumatic conditions, the presence of certain antibodies, abnormalities in the system that regulates the body's immune response and frequent pulmonary hypertension[1–3].

HIGHLIGHTS

- There are limited data concerning the association between mixed connective tissue disease, and ovarian cancer.
- Our patient was diagnosed to have mixed connective tissue disease, in addition to amass at the right ovary though she had no risk factors for developing ovary cancer.
- It is important to keep in mind the development of malignancy during mixed connective tissue disease course.

This condition has many symptoms, including: arthritis, Raynaud's phenomenon, skin changes, loss of hair ,muscle weakness, dysphagia, peripheral neuropathy, lung, and renal involvement[3].

Its diagnosis can be challenging. There is considerable overlap between the symptoms. Besides, laboratory markers are not specific and may occur in different diseases. Thus, many patients do not carry a well-defined diagnosis[1,2].

There is no one widely accepted set of classification criteria; several criterion sets have been tested successfully, including Sharp's criteria, the Kasukawa diagnostic criteria, and the Alarcón-Segovia criteria[3,4].

Diagnostic criteria may help define patients with MCTD, but in several cases, patients may not fulfil diagnostic criteria at their initial presentation. Patients with an unclassifiable clinical picture

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are usually diagnosed as having "undifferentiated connective tissue disease" (UCTD)[1,5].

Corticosteroids, especially when given early in the course of the disease, can be helpful in managing the symptoms. Among patients requiring long-term glucocorticoids, hydroxychloroquine or methotrexate is reasonable. Intravenous immunoglobulin may also have a role in patients with resistant thrombocytopenia or severe eruptive skin disease[2].

The overall 10-year survival rate is about 80%, but the prognosis depends largely on which manifestations predominate[6].

MCTD can cause life-threatening complications such as pulmonary hypertension, kidney failure, heart attack, infections, and stroke or intestinal perforation[1,2,5].

Limited case reports revealed the association between MCTD and cancer, like lymphoma, lung cancers, and others[2].

Case presentation

A 22-year-old Syrian female, married, housewife, non-smoker - no alcohol, body mass index 25, presented with enlargement of the abdomen and oedema of the lower extremities, gradually started 25 days ago, in the out-clinic of Al-Moussat University Hospital in 2022. By reviewing a doctor who conducted an abdominal ultrasound, which revealed a heterogeneous high-echo mass with hypoechoic areas at the expense of the right ovary.

The complaint was accompanied by the progression of dyspnoea on light exertion, with orthopnea without paroxysmal nocturnal pain, and thoracic-parietal pain without coughing, sputum or hemoptysis. No other symptoms were found at that time except of Raynaud phenomenon and dysphagia.

The patient had been diagnosed by an external rheumatologist to have rheumatoid arthritis, according to the ACR/EULAR2019 Criteria[3], as she had arthritis of small hands and feet, wrists and knees, morning stiffness more than one hour, in addition to positive rheumatic factor, and Anti-CCP. She was treated with 7.5 mg/week MTX for 6 months. There were no other complaints. She had no other previous medical history, and her brother had lupus.

On presentation; her vital signs were: blood pressure: 13/8 left upper arm, pulse: 102/min/m/m, respirations: 20/min, temperature: 37.4°C, and saturation: 94%.

Physical examination revealed: pallor on the conjunctiva, slight jugular congestion.

Lung examination showed subsided in the lower two-thirds of the pulmonary, with percussion and faintness in vibrations.

Abdominal examination: liver span: 13 cm, surgical scar, below the navel, with purulent exudate. Lower limb oedema, and degree 3 depths 2 extensions.

Rheumatologic examination revealed: inability to make a hand grip, synovitis of the second and third PIP of the right hand, button deformation with the fifth finger of hands, negative squeeze test, and limited range of movement of both wrists (Fig. 1). The remaining examination was unremarkable.

The laboratory tests are shown in Table 1.

CPK; 987u, aldolase7.1u The immune profile: antinuclear antibody: positive at 1/320, anti-ds DNA: positive at 1/160, antinuclear ribonucleoprotein (anti-RNP) positiveat32U (n < 20), lupus anticoagulant:51(positive), anti Cardiolipine IgM:17.7 (negative), anti Cardiolipine IgG:21.8 (positive), and anti B2 Glycoprotein 1 IgM:6.5 (negative).

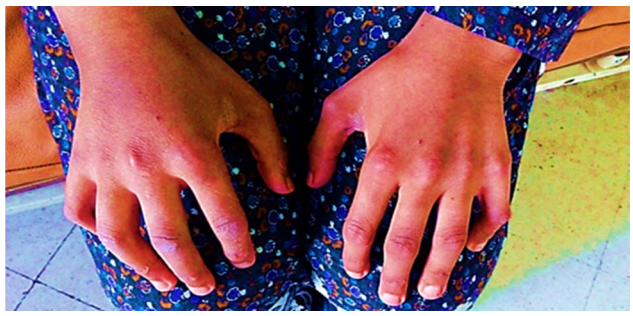

Figure 1. Rheumatologic examination in hands.

The virology profile of hepatitis B, hepatitis C, and AIDS viruses were negatives Urinary analysis showed proteinuria + + +, red blood cells 5–6 cells, and white blood cells 3–4. Urinary protein excretion was 1625 mg/24 h (urine volume 2150 ml), creatinine 725.25 mg, and creatinine clearance of 94 ml/mi. Urine culture was negative.

Electrocardiogram (EKG) showed rregular sinusoidal, normal axis, HR: 100, no significant schematic shifts (Image 1) Chest X-ray showed: symmetrical inspiratory, large cardiorespiratory, closure of the diaphragmatic angles, and bilateral pleural effusion, without pulmonary infiltrations (Image 2) Anterior and posterior hand X-ray revealed: ankylosis of the PIP joints, decreased density around the articular surfaces (Image 3).

Echocardiography revealed left ventricle: Concentric wall thickness, diaphragm thickness, and posterior wall thickness. EF = 73%. Mild mitral insufficiency, pulmonary pressure 35–40 mmHg, and pericardial effusion measuring 1 cm. A pleural effusion was observed with a large quantity surrounding the heart.

Abdominal and pelvic echo showed an amount of free fluid around the liver and in Morrison's sinus, and in the pelvis, with the presence of a heterogeneous mass on the right ovary.

Thoracic-abdominal and pelvic axial tomography with injection (before cyst excision) showed left pleural effusion of small size with right pleural reaction, no pericardial effusion, abundant ascites in the abdomen and pelvis, a heterogeneous mass with a diameter of 5 × 6 cm at the expense of the right ovary, which reinforces the contrast material in a heterogeneous and circumferential manner.

Table 1

The laboratory tests

WBC	4.8	Ur	11	Na	141
N/L	73/21	Cr	0.9	K	3.14
RBC	4.3	LDH	236	PT	85%
HB	11.3	TP	5.7	PT/INR	1.1
Ht	34.8	Alb	2,5	Reticulocyte	0.8
MCV	80.8	Alt	8	Coombs D	Neg
MCH	26.2	Ast	20	Coombs In	Pos +
PLT	201	TB	0.4		
ESR	80	DB	0.2	RF	29.8
CRB	3 mg/dl	Glu	81	Anti-CCP	1.3
		C3	23.7	C4	3.9
Fe	17	TIBC	116	Transferrin saturation	15
Ferritin	2191	B9	15.1	B12	316

CRP, C reactive protein; ESR, erythrocyte sedmenation rate; HB, haemoglobin; Ht, Hematocrit; MCH, mean corpuscular volume and hemoglobin; Neg, negative; N/L, neutrophils/lymphocyte; Pos, positive; PLT, platelet; PT, prothrombin time; RBC, red blood cell; TIBC, total iron-binding capacity; WBC, white blood cell.

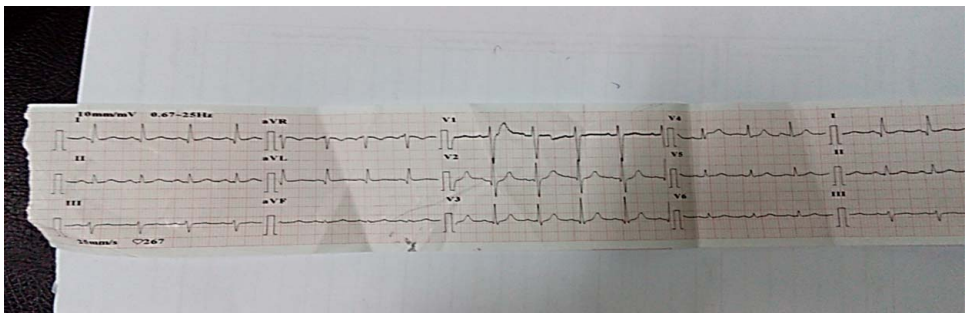

Image 1. Electrocardiogram (EKG).

Echo Doppler of the portal vein was normal (In the context of the study of ascites).

Diagnostic pleurocentesis with transfusion of bacterial cultures on the fluid, a high-resolution computed tomography procedure. Pleurisy fluid is an exudate, WBC = 1480.70% neutrophils, 30% lymphocyte, TP 2.3, glucose 70, and lactate dehydrogenase 279. Koch bacillus test with pleurisy fluid: negative. Examination of abnormal cells in pleural fluid: negative. bacterial culture was negative.

A kidney biopsy revealed diffuse mesangial proliferation with segmental necrotizing crescent formation, indicating class III lupus nephritis.

The mass was removed surgically, and a biopsy was taken. The biopsy showed: nuclear pleomorphic cells and tubular proliferation. Immunohistology revealed that the tumour cells were positive for both p53 and cytokeratin 7, and negative for oestrogen receptor, and cyclin-dependent kinase 2, which is compatible with ovarian high-grade serous adenocarcinoma.

After the lumpectomy, a course of solumedrol 1 g/IV/3 days was applied, and then continue with 60 mg/day oral predlone.

One week postoperatively, she developed an infection at the surgical site, and she was placed on tasocine + ciprofloxacin, according to the result of a wound swab culture. Later on discharge, she was taken 25 mg/day predlone, and methotrexate 10 mg.

Discussion

MCTD is a disease of unknown cause, characterized by the presence of high titres of anti-U1 RNP with clinical features of RA, SLE, DM, PM, and scleroderma[1].

MCTD occurs in all ethnicity, especially in adolescence and the 20 s. About 80% of people who have the disease are women[2], which is compatible with our case.

The cause of MCTD is unknown, although several factors suggest that mixed connective tissue disease is a distinct disorder in its own right[2].

These include symptoms shared by several rheumatic conditions, the presence of certain antibodies, abnormalities in the system that regulates the body's immune response and frequent pulmonary hypertension[1–3]. This condition has many symptoms, including: arthritis, Raynaud's phenomenon, skin changes, loss of hair ,muscle weakness, dysphagia, peripheral neuropathy, lung and renal involvement[3].

One of the most common clinical presentations is arthralgia, and symmetrical arthritis that often involves metacarpophalangeal and proximal interphalangeal, wrists, metatarsophalangeal, knee, elbow, and ankle[7], as in our case.

There is no one widely accepted set of classification criteria; several criterion sets have been tested successfully, including Sharp's criteria, the Kasukawa diagnostic criteria, and the Alarcón-Segovia criteria[3,4], with different sensitivity and specificity[3,4], like how we diagnosed our patient. She had arthritis, Raynaud's phenomenon, dysphagia, and renal involvement, in addition to the positivity of antinuclear antibody, anti-RNP, anti-ds DNA, lupus anticoagulant , and anti Cardiolipine IgG, a Urinary analysis showed proteinuria + + + , red blood cells 5–6 cells, and white blood cells 3–4. Urinary protein excretion was 1625 mg/24 h.

Corticosteroids, especially when given early in the course of the disease, can be helpful in managing the symptoms. Among patients requiring long-term glucocorticoids, Hydroxychloroquine or

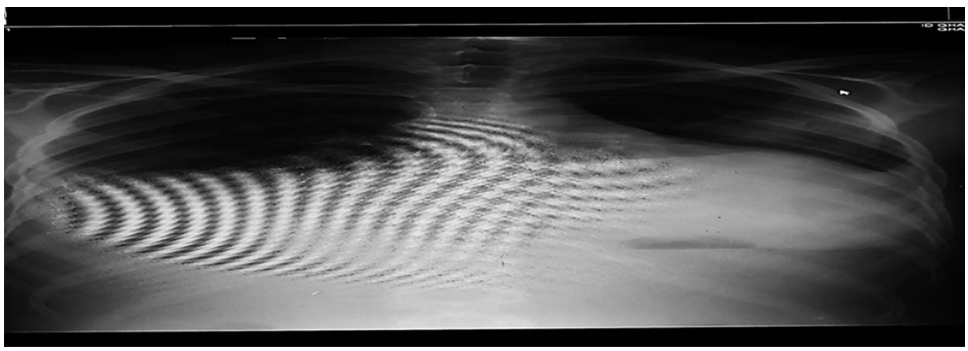

Image 2. Chest X-ray.

Image 3. X-ray of hands.

Methotrexate is reasonable, as we treated our patient . Intravenous immunoglobulin is used in patients with resistant thrombocytopenia or severe eruptive skin disease[2,8].

The overall 10-year survival rate is about 80%, but the prognosis depends largely on which manifestations predominate[6]. Mixed connective tissue disease can cause life-threatening complications such as pulmonary hypertension, kidney failure, heart attack, infections, and stroke or intestinal perforation[1,2,5].

Limited case reports revealed the association between MCTD and cancer, like lymphoma, lung cancers, and others[2].

There are reports supporting the association between autoimmune diseases, especially RA, SLE, and DM, and an elevated risk of malignancy[9–11]. Meanwhile, limited cases suggest the association between MCTD and malignancies[5].

However, the exact pathogenesis of the association between MCTD and malignancy remains unclear. This may be due to underlying dysregulation of the immune system or treatment that is in patients with autoimmune diseases, as immunosuppressive drugs and biological agents may also be carcinogenic[12]. Inflammation in the setting of autoimmunity may serve as a trigger for malignancy. This echoes the hypothesis made by Rudolf Virchow who, in 1863, stated that the origin of cancer at different sites was due to chronic inflammation[13]. In addition, chronic antigenic stimulation of B-lymphocytes present in autoimmune disorders might eventually lead to clonal proliferation and defective immune surveillance in autoimmunity may lead to pre-selection of specific B-cell clones, thus triggering cancer[13]. Moreover, some studies suggested shared genetic susceptibility for both conditions[12,13].

The relationship among autoantibodies, inflammation and spontaneous tumour development can easily be tested. Tumour-associated antigens may be produced by inflammatory cells and their production may be increased in rheumatoid arthritis and other autoimmune diseases[14,15,16]. Transcriptional intermediary factor gamma antibody (TIF1γ), which is considered as precancerous factor[17].

Table 2

Data of ovarian cancer in MCTD

Study	No. patients	Type of immune disease
Black KA, Zilko PJ, Dawkins RL, Armstrong BK, Mastaglia GL.	40 patients 11 male 29 female	Polymyositis SLE RA PSS MCTD;1women, ovarian cancer

MCTD, mixed connective tissue disease; PSS, progressive systemic sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

To date, there have been case reports of MCTD being associated with lung cancers, lymphoma, ovarian cancer, non-Hodgkin's lymphoma, thymic carcinoma, hepatocellular carcinoma, and in one case, gastric and uterine cervix cancers[1–3,8,9].

There are limited data concerning the association between MCTD, and ovarian cancer, like Black *et al*.[15] study which reported an association of MCTD with an increased risk of cancer, but the sample size was relatively small and may be biased in favour of the inclusion of patients from MCTD with complications. He followed 40 patients with MCTD, the ovarian cancer was found in one women out of 29, and Zoltán Szekanecza and colleagues Study that showed an autoimmune disease usually develops in younger patients, and malignancies, especially lymphproliferative disorders, usually occur in elderly patients with long disease duration. Sustained inflammatory activity seems to be the primary risk factor for malignancies in autoimmune diseases[16]. By contrast, Wouters and colleagues, meta-anlysis showed a lower incidence and risk of ovarian cancer was found in patients with systematic lupus erythematous, multiple sclerosis. No conclusions could be drawn on mortality or the influence of immunosuppressive drugs used in the treatment of autoimmune diseases and the incidence of ovarian cancer[18]. The data of these case report are showed in Table 2.

The difference of our case is that our patient had no risk factors for developing ovary cancer like positive family history, older-than 40 years, obesity, smoking, and some treatments[19]. On the contrary, our patient was a young, non-smoker, without any previous treatment before the RA diagnosis was taken, and finally, she had 3 children with full-term pregnancy, and well health.

Conclusions

Our case showed that the patient had no risk factors for developing ovary cancer. On the contrary, our patient was a young, non-smoker, without any previous treatment before the RA diagnosis was taken, and finally, she had three children with full-term pregnancy, and well health. This case highlights the importance of maintaining a high index of suspicion for malignancy in MCTD patients. However, further investigation on the role of the immune system in the development of ovarian cancer in women with autoimmune diseases including MCTD remains necessary.

Ethical approval

Ethical committee of Faculty of medicine. Damascus University. Syria NumberCV75461.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical Institutional approval is not required for this case study, because we used the patient data without any identification.

Source of funding

None.

Author contribution

N.K. wrote the discussion, M.A. wrote the abstract, L.H. wrote the case presentation, A.O.A. wrote the background and references. M.K. supervised and approved the final file.

Conflicts of interest disclosure

The authors have no conflicts of interest to declare.

Research registration unique identifying number (UIN)

MCTD and ovarian cancer, 9128 https://www.researchregistry.com/browse-the-registry#home/.

Guarantor

Prof Maysoun Kudsi.

Data availability statement

Data are available upon reasonable request.

Provenance and peer review

I agree.

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