Case report

Pneumocystis jirovecii pneumonia complicating methotrexate treatment in a patient with low-risk post-molar gestational trophoblastic neoplasia: A case report and review of the literature

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ABSTRACT

Low-risk gestational trophoblastic neoplasia (GTN) is generally treated with single agent chemotherapy, including methotrexate (MTX) or dactinomycin. We present a case of a patient with low-risk GTN who underwent single agent MTX therapy, developed *Pneumocystis jirovecii* pneumonia (PJP), recovered, and ultimately completed consolidation treatment for GTN on single agent MTX. While MTX administration is associated with an increased risk of PJP, this association is best described in rheumatology literature. This is the first case of PJP complicating MTX therapy within the gynecologic oncology literature.

1. Introduction

Gestational trophoblastic disease (GTD) is a group of interrelated tumors that arise from abnormal fertilization events and include benign conditions (complete hydatidiform mole, partial hydatidiform mole, placental site nodule) and malignant conditions (invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic tumor) (Horowitz, 2021; Ngan, 2018). The malignant conditions are collectively termed gestational trophoblastic neoplasia (GTN). A diagnosis of GTN does not require histologic confirmation, and is the only malignancy diagnosed based on a serum assay, specifically human chorionic gonadotropin (hCG) (Horowitz, 2021; Lurain, 2010).

Post-molar GTN is diagnosed based on criteria from International Federation of Obstetrics and Gynecology (FIGO) and World Health Organization (WHO) (Table 1) (Ngan, 2018). The risk of post-molar GTN is 1–5 % for partial molar pregnancies and 15–20 % for complete molar pregnancies (Lurain, 2010).

Treatment decisions are made based on a risk stratification system (low-risk, high risk, ultra-high risk) which account for FIGO anatomic stage and WHO prognostic scores. A score of 0–6 suggests low-risk of resistance to single agent chemotherapy. Treatment for post-molar, low-risk GTN can include consideration of secondary uterine curettage (Osborne, 2016); single agent chemotherapy with MTX or dactinomycin (Act-D), or hysterectomy in the setting of no desire for future fertility

(Horowitz, 2021).

MTX, an antimetabolite and immunomodulatory agent with multiple indications for use, can cause pulmonary toxicity in the form of pneumonitis, organizing pneumonia, pulmonary fibrosis, pleural effusion, pulmonary infections, or lymphoproliferative disease (Agarwal, 2022). *Pneumocystis jirovecii* is a unique opportunistic fungus that can cause a life-threatening pneumonia in the setting of immunodeficiency and is traditionally seen in patients with human immunodeficiency virus (HIV) (Ma et al., 2018). This observation has warranted the use of antibiotic prophylaxis in severe immunodeficiency (CD4 < 200 cells/microL or CD4 count < 14 percent) or in the setting of chronic conditions of lymphodepletion (Kaplan, 2009). While MTX treatment is not an indication for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis, MTX can be a risk factor for the development of PJP.

Due to the frequency and chronicity of use, most cases of PJP complicating MTX therapy have been reported in the rheumatology literature, including in the treatment of rheumatoid arthritis, inflammatory myopathies, lupus, and granulomatosis with polyangiitis (Schmajuk, 2019; Mecoli, 2017; Mori and Sugimoto, 2015). To date, the gynecologic oncology and medical oncology literature has limited documented cases of MTX-associated pneumonitis, but no cases of PJP (Agarwal, 2022; Zhang, 2008). We present a case of a patient with low-risk GTN who underwent single agent MTX therapy, developed PJP, recovered, and ultimately completed consolidation treatment for GTN

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Table 1
FIGO/WHO criteria for diagnosis of post-molar Gestational Trophoblastic Neoplasia (GTN).

FIGO Post-Molar GTN criteria
Plateauing of hCG +/− 10 % for 4 consecutive values over 3 weeks (i.e., days 1, 7, 14, 21)
A rise in hCG levels of ≥ 10 % for 3 values over 2-week period (i.e., days 1, 7, 14)
Histologic diagnosis of choriocarcinoma or clinical and/or radiologic evidence of metastases

WHO Prognostic Scoring System

Risk Factor	Score			
	0	1	2	4
Age (Years)	<40	≥40		
Antecedent Pregnancy	Mole	Abortion	Term	
Interval*(months)	4	4 to 6	7 to 12	>12
Pre-treatment serum hCG (mIU/mL)	$<10^3$	10^3 to 10^4	10^4 to 10^5	$>10^5$
Largest tumor (including uterus)	<3cm	3 to 4 cm	≥5cm	–
Site of metastases	Lung	Spleen, Kidney	GI tract	Brain, liver
Number of metastases	–	1 to 4	5 to 8	>8
Prior failed chemotherapy	–	–	Single drug	≥2 drugs

FIGO Staging of GTN

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina)
Stage III	GTN extends to the lungs, with or without genital tract involvement
Stage IV	All other metastatic sites

FIGO: International Federation of Gynecology and Obstetrics; WHO: World Health Organization; hCG: human chorionic gonadotropin; GI: gastrointestinal. *Interval (in months) between end of antecedent pregnancy and start of chemotherapy.

on single agent MTX.

2. Case presentation

A 35-year-old non-Hispanic white female gravida 2 para 1 with history of Horner's syndrome and vertebral pseudoaneurysm presented to care for pregnancy confirmation and was found to have a hCG level of 258,000 IU/L. She had a history of one uncomplicated term vaginal delivery and no prior history of gestational trophoblastic disease. Pelvic ultrasound findings were concerning for molar pregnancy, including a disorganized endometrium with scattered fluid and cystic spaces. She underwent dilation and curettage and final pathology described hydropic villi and trophoblastic proliferation, consistent with complete molar pregnancy. A plan was made to monitor plasma hCG levels once per week until negative. A levonorgestrel intrauterine device (IUD) was placed for contraceptive purposes. Her hCG levels on post-operative days 14, 21, and 28 were 2906, 6328, and 8009 IU/L respectively. Of note, a single dose of MTX 50 mg/m2 on post-operative day 21 was given by her general gynecologist following the initial rise of hCG. A chest radiograph and computed tomography (CT) abdomen and pelvis were performed which were negative for extrauterine disease. Her hCG ultimately peaked to 10,371 IU/L prior to initiating a definitive MTX treatment plan. She met criteria for post-molar low-risk GTN based on her rising hCG with a WHO prognostic score of 2 (pre-treatment hCG 10^4–10^5) and FIGO Stage I (Table 1). Given these findings, she and was referred to a medical oncologist.

As a derivation of the MTX 1 mg/kg intramuscular (IM) every other day for 4 days with leucovorin rescue (Table 2), our patient underwent six two-week cycles of MTX 1 mg/kg IM twice weekly with leucovorin rescue with a medical oncologist. Her hCG levels were measured with

Table 2
Single-agent Methotrexate regimens for low-risk gestational trophoblastic neoplasia (Lurain, 2010).

Methotrexate Regimens	Primary remission rates
0.4 mg/kg (max 25 mg) IV (preferred) or IM on days 1, 2, 3, 4, 5, repeat every 14 days	87–93 %
1 mg/kg IM on days 1,3,5,7 with leucovorin on days 2, 4, 6, 8, repeat every 14 days	74–90 %

each cycle and were down trending, however at the start of cycle 6, her hCG rose to 1413 from 1225 IU/L two weeks prior. This prompted a repeat transvaginal ultrasound and CT abdomen and pelvis notable for thickening of the endometrium. With continued treatment, hCG levels proceeded to decline, and after two additional cycles of MTX as scheduled above, her hCG ultimately dropped to 11 IU/L. To our knowledge, hysterectomy was not offered as part of her treatment options before undergoing MTX chemotherapy.

At this time, a second opinion was obtained at our institution. We did reconfirm her desire for future childbearing upon transfer to our care. A plan was made to continue MTX therapy using 0.4 mg/kg days 1–5 until hCG at lower limit of normal, followed by three cycles of consolidation therapy.

On cycle 9 day 11, she presented to the emergency department with fever, rigors, and shortness of breath with ambulation. She was febrile to 38.4C, tachypneic, tachycardic, and hypoxemic, requiring supplemental oxygen. Her pulmonary exam demonstrated decreased breath sounds, bilaterally. Her white blood cell count was 10.2×10^9/L and her ANC was 8.8×10^9/L. A chest radiograph was performed and demonstrated patchy opacities in the right lower and left mid to upper lung zone, concerning for multifocal infection (Fig. 1). She was admitted to the hospital with a presumed diagnosis of community acquired pneumonia and was started on amoxicillin/clavulanate and azithromycin. Although MTX induced pneumonitis was in the differential diagnosis, it is typically a diagnosis of exclusion after first ensuring no infectious etiology. Further, radiographic findings in MTX induced pneumonitis include bilateral, symmetric, reticular opacities at the lung bases with or without honeycombing (Bedrossian Cw Fau - Miller et al., 1979). In addition, there was no laboratory evidence of MTX induced cytopenias to suggest an acute immunodeficiency syndrome as the cause of her presentation. On hospital day 3, her clinical course worsened with an increase in oxygen requirement from 2L to 6L high flow nasal cannula. Concerned that she was not improving despite antibiotics, an infectious disease consult was obtained which prompted additional evaluation and treatment adjustments. Recommendations included sputum cultures, CT chest, *Pneumocystis jirovecii* direct fluorescent antibody (DFA) sputum test and PCR, serum beta-d glucan (non-invasive screening for invasive fungal infection), urine histoplasma antigen, and serum QuantiFERON gold. Amoxicillin/clavulanate was discontinued and ceftriaxone was initiated with continuation of azithromycin to follow a more aggressive inpatient treatment approach with intravenous antibiotics. By hospital day 5, she had significant improvement in her pulmonary function (weaned from 8L to 2.5L nasal canula) and was discharged on amoxicillin/clavulanate and azithromycin for 5 days. Pending laboratory tests prior to discharge were a sputum *Pneumocystis jirovecii* PCR, serum beta-d glucan, and urine histoplasma antigen.

She was readmitted the day following discharge given a worsening oxygen requirement at home and a positive beta-d-glucan test, concerning for an invasive fungal etiology. Amoxicillin/clavulanate and azithromycin were discontinued. She was started on isavuconazole and trimethoprim-sulfamethoxazole. On hospital day 2, she became acutely worse and required transfer to the intensive care unit for 45L/60 % FiO2 heated high flow supplemental oxygen therapy. She was given a steroid taper and broad-spectrum antibiotics were initiated, including linezolid and piperacillin/tazobactam. On hospital day 4, her *Pneumocystis*

A. Chest radiograph with patchy opacities in the right lower and left mid to upper lung zone suspicious for multifocal infection. Hospital Day 1


B. Chest radiograph with interval increase in patchy bilateral airspace opacities, concerning for

pneumonia. Hospital Day 2

Fig. 1. A. Chest radiograph with patchy opacities in the right lower and left mid to upper lung zone suspicious for multifocal infection. Hospital Day 1B. Chest radiograph with interval increase in patchy bilateral airspace opacities, concerning for pneumonia. Hospital Day 2C: Chest computed tomography demonstrated multifocal airspace and ground glass opacities most in keeping with pneumonia. Hospital Day 3.

jirovecii PCR resulted as positive, confirming a diagnosis of PJP; by this time, she had demonstrated remarkable clinical improvement. All antibiotics except trimethoprim-sulfamethoxazole were discontinued. On hospital day 5, she was discharged with normal vital signs and a plan to take trimethoprim-sulfamethoxazole and prednisone taper for 21 days. Following completion of this course, she was continued on PJP prophylaxis while finishing consolidation treatment for GTN.

With shared decision making between infectious disease colleagues, our clinical pharmacist, and the patient, we discussed the nuances of her continued treatment for GTN in the setting of her recent PJP. Given the risk for severe myelosuppression, mucositis, and nephrotoxicity with concurrent MTX and trimethoprim-sulfamethoxazole, we considered a treatment change with Act-D in place of MTX versus selecting an alternative prophylaxis for PJP. The decision was made to complete the 21-day course of trimethoprim/sulfamethoxazole while holding MTX infusions during this time. With the expertise from infectious disease, prophylaxis was changed to dapsone after negative glucose-6-phosphate deficiency (G6PD) testing to minimize the risk of hemolytic anemia. Plasma hCG levels were monitored weekly while MTX infusions were held and noted to be < 1 IU/L. After a period of 96 h following her last dose of trimethoprim/sulfamethoxazole, it was deemed safe to receive MTX per consultation with our pharmacist. While initial plan had been for three consolidative cycles (Lybol, 2012), she completed two consolidative cycles with persistent negative hCG serum testing. She
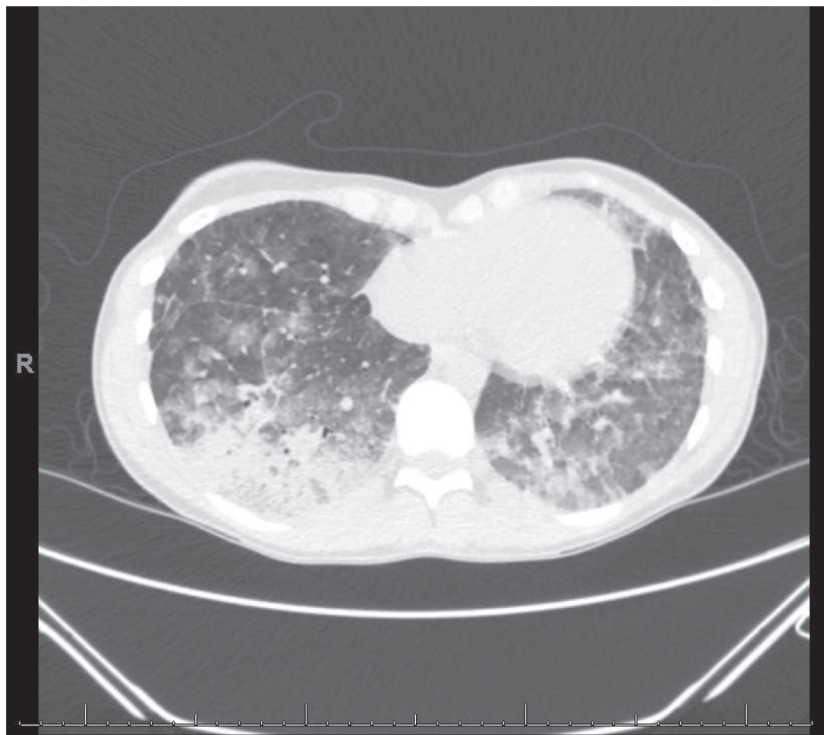
C: Chest computed tomography demonstrated multifocal airspace and ground glass opacities

most in keeping with pneumonia. Hospital Day 3

Fig. 1. (*continued*).

completed monthly hCG levels for 12 months with her levonorgestrel IUD in place and without evidence of recurrence. Her complete hCG trend can be found on Fig. 2. She currently has a viable pregnancy as of the writing of this manuscript. She has no chronic respiratory comorbidities.

3. Discussion

While MTX is used for multiple indications from rheumatologic disorders to GTN, the potential for MTX-induced pulmonary toxicity in the form of pneumonitis, organizing pneumonia, pulmonary fibrosis, pleural effusion, or pulmonary infections including PJP are rarely seen within the gynecologic oncology literature. We present a novel case within our field of a patient who developed PJP while receiving MTX for low-risk, post-molar GTN.

We recommend that patients who present with new or persistent respiratory complaints while on MTX be carefully evaluated and monitored due to risk of acute decompensation, as this young and otherwise healthy patient clinically declined during her first admission while on the first-line treatment for PJP. Further, we recommend obtaining consultation from infectious disease for a multi-disciplinary approach given need for monitoring and prophylaxis for months following diagnosis.

Trimethoprim-sulfamethoxazole is the recommended treatment for PJP, including in patients with a prior allergy or hypersensitivity aside from anaphylaxis, in which case desensitization is recommended (Cooley, 2014). High dose MTX is a contraindication to treatment with trimethoprim-sulfamethoxazole given the increased risk of severe myelosuppression (Al-Quteimat & Al-Badaineh, 2013). Alternative treatment and prophylaxis can be given with dapsone, pentamidine or atovaquone, however we recommend collaboration with infectious disease to determine the preferred agent (Cooley, 2014). G6PD testing should be considered for all patients undergoing PJP prophylaxis with

dapsone given the risk of hemolytic anemia. While trimethoprim-sulfamethoxazole can also be associated with hemolytic anemia, this risk is much lower compared to dapsone and GDPD testing is not indicated for patients prescribed trimethoprim-sulfamethoxazole (Belfield and Tichy, 2018).

Since our patient was discharged on trimethoprim-sulfamethoxazole, we subsequently recommended either changing her chemotherapy to Act-D versus using an alternative prophylaxis for PJP. Rates of remission with recommended MTX and Act-D regimens are near 90 % (Soper, 1994; Roberts and Lurain, 1996; Schink, 2020; Lawrie, 2016). While a Cochrane review favored Act-D over MTX in terms of efficacy, many practitioners favor MTX due to ease of administration and improved side effect profile (Lawrie, 2016). A phase III trial was published comparing multi-day MTX to pulse-Act-D, however closed early due to low accrual (Schink, 2020). After discussing the side effect profile of Act-D, our patient desired to continue MTX if safe and feasible while changing her prophylaxis to an alternative agent. Though she would not be able to receive MTX while receiving trimethoprim/sulfamethoxazole and require a 96-hour period before restarting MTX, we monitored hCGs weekly while she completed initial treatment with trimethoprim/sulfamethoxazole and before beginning prophylaxis. If her hCGs had increased during this time, we would have altered our recommendation to proceed with Act-D.

4. Conclusion

We present a unique case of PJP in a patient undergoing treatment for low-risk GTN. This is a novel case within the gynecologic oncology literature. Medical oncologists and gynecologic oncologists should be aware of this rare but potentially life-threatening infection that our patients on MTX are at an increased risk to develop.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the
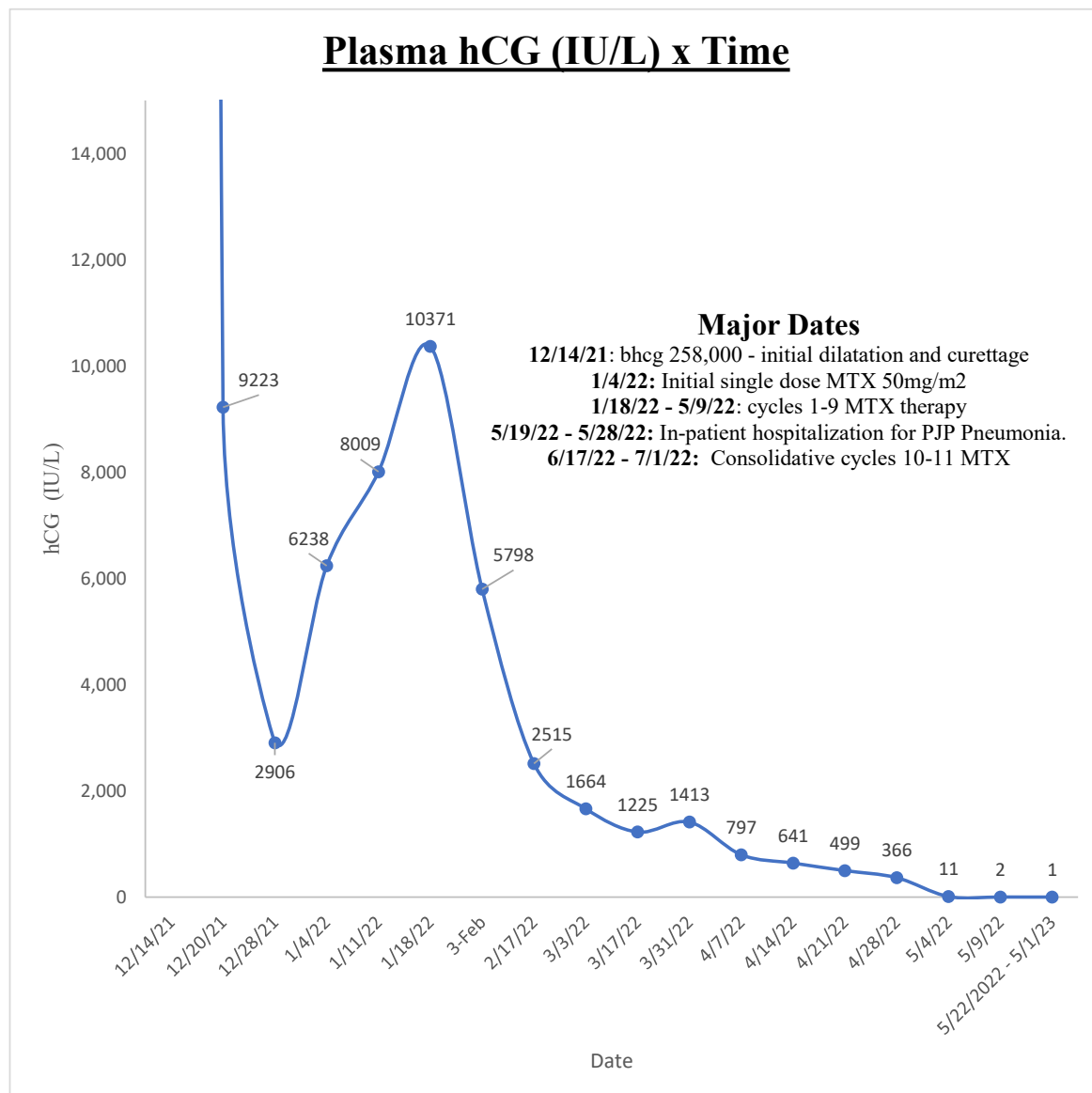
Fig. 2. hCG trend over time with key major events in the patient's care while undergoing treatment for low-risk gestational trophoblastic neoplasia.

written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Hector S. Porragas-Paseiro: Conceptualization, Writing – review & editing. **Steven Johnson:** Supervision. **Lindsay Brubaker:** Conceptualization, Supervision, Writing – review & editing. **Brooke E. Sanders:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Agarwal, M., et al., 2022. Methotrexate pneumonitis in a patient with gestational trophoblastic neoplasia. Afr. J. Thorac. Crit. Care Med. 28 (3).

Al-Quteimat, O.M., Al-Badaineh, M.A., 2013. Methotrexate and trimethoprim-sulphamethoxazole: extremely serious and life-threatening combination. J. Clin. Pharm. Ther. 38 (3), 203–205.

Bedrossian Cw Fau - Miller, W.C., M.A. Miller Wc Fau - Luna, and M.A. Luna, 1979 *Methotrexate-induced diffuse interstitial pulmonary fibrosis.* (0038-4348 (Print)).

Belfield, K.D. and E.M. Tichy, 2018, *Review and drug therapy implications of glucose-6-phosphate dehydrogenase deficiency.* (1535-2900 (Electronic)).

Cooley, L., et al., 2014. Consensus guidelines for diagnosis, prophylaxis and management of Pneumocystis jirovecii pneumonia in patients with haematological and solid malignancies, 2014. Intern. Med. J. 44 (12b), 1350–1363.

Horowitz, N.S., et al., 2021. Epidemiology, diagnosis, and treatment of gestational trophoblastic disease: A Society of Gynecologic Oncology evidenced-based review and recommendation. Gynecol. Oncol. 163 (3), 605–613.

Kaplan, J.E., et al., 2009. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm. Rep. 58 (RR-4), 1–207 quiz CE1-4.

Lawrie, T.A., et al., 2016. First-line chemotherapy in low-risk gestational trophoblastic neoplasia. Cochr. Database Syst. Rev. 2016 (6), CD007102.

Lurain, J.R., 2010. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am. J. Obstet. Gynecol. 203 (6), 531–539.

Lybol, C., et al., 2012. Relapse rates after two versus three consolidation courses of methotrexate in the treatment of low-risk gestational trophoblastic neoplasia. Gynecol. Oncol. 125 (3), 576–579.

Ma, L., Cissé, O.H., Kovacs, J.A., 2018. A molecular window into the biology and epidemiology of pneumocystis spp. Clin. Microbiol. Rev. 31 (3), e00009–e18.

Mecoli, C.A., et al., 2017. Pneumocystis jiroveci pneumonia in rheumatic disease: a 20-year single-centre experience. Clin. Exp. Rheumatol. 35 (4), 671–673.

Mori, S., Sugimoto, M., 2015. Pneumocystis jirovecii Pneumonia in rheumatoid arthritis patients: risks and prophylaxis recommendations. Clin .Med. Insights. Circul. Respirato. Pulmon. Med. 9 (Suppl 1), 29–40.

Ngan, H.Y.S., et al., 2018. Update on the diagnosis and management of gestational trophoblastic disease. Int. J. Gynecol. Obst. 143 (S2), 79–85.

Osborne, R.J., et al., 2016. Second curettage for low-risk nonmetastatic gestational trophoblastic neoplasia. Obst. Gynecol. 128 (3), 535–542.

Roberts, J.P., Lurain, J.R., 1996. Treatment of low-risk metastatic gestational trophoblastic tumors with single-agent chemotherapy. Am. J. Obst. Gynecol. 174 (6), 1917–1923 discussion 1923–4.

Schink, J.C., et al., 2020. An international randomized phase III trial of pulse actinomycin-D versus multi-day methotrexate for the treatment of low risk gestational trophoblastic neoplasia; NRG/GOG 275. Gynecol. Oncol. 158 (2), 354–360.

Schmajuk, G., et al., 2019. Pneumocystis jirovecii pneumonia (PJP) prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. Semin. Arthritis Rheum. 48 (6), 1087–1092.

Soper, J.T., et al., 1994. 5-day methotrexate for women with metastatic gestational trophoblastic disease. Gynecol. Oncol. 54 (1), 76–79.

Zhang, D., et al., 2008. Two rare cases of methotrexate-induced pneumonitis and pleurisy in patients with gestational trophoblastic neoplasms. Eur. J. Gynaecol. Oncol. 29 (4), 390–392.