Annals of Clinical and Medical Case Reports

Case Report ISSN 2639-8109 | Volume 7

The Lethal Effect of COVID-19 on Pregnancy Associated with Neuroendocrine Neoplasm (NEN)

Laura ȘB[1*], Tiberiu P[2] and Rareș G[3]

[1]University of Oradea, Doctoral School of Biomedical Science, 1st University Street, 410087, Oradea, Romania

[2]County Emergency Clinical Hospital from Oradea, Romania

[3]University of Oradea, Medicine and Pharmacy Faculty, Romania

[*]Corresponding author:

Șugac Bianca Laura,
University of Oradea, Doctoral School of Biomedical Science, 1st University Street, 410087, Oradea, Romania,
Tel: 0040-742066262,
E-mail: biancalaura2491@yahoo.com;
rares.gherai@gmail.com

Received: 01 Sep 2021
Accepted: 15 Sep 2021
Published: 20 Sep 2021

Keywords:

Pregnancy; Maternal death; COVID-19; SARS-CoV-2; ARDS; Metastatic ovarian cancer; Pancreatic neuroendocrine malign tumor

Citation:

Laura ȘB, The Lethal Effect of COVID-19 on Pregnancy Associated with Neuroendocrine Neoplasm (NEN). Ann Clin Med Case Rep. 2021; V7(8): 1-5

1. Abstract

From December 2019, starting from Whuan, COVID-19 pandemic was threatening the entire world population with a major lethal potential. This new infection, with SARS-CoV-2, induces and maintains in human body a significant disturbance in the homeostasis of immune reactions followed by a multiorganic morphological and pathophysiological alterations. The new coronavirus (SARS-CoV-2) was identified and certified as pandemic trigger. With millions of people infected, hundreds of thousands of whom have died worldwide, there is now a maximum urgent need to develop a series of effective prophylactic and curative therapeutic tools essential to save human lives. Especially because currently, we do not yet have an effective anti-COVID-19 curative panacea, and obstetrically, we do not yet have sufficient certified informative details about the prevalence, semiology and predictable complications of intra- and post- gestational infection with SARS-CoV-2 in metastatic ovarian cancer of a neuroendocrine neoplasm (NEN). Neuroendocrine neoplasms occur in a variety of morphological sites, including pulmonary, gastric, intestinal, pancreatic, colic, rectal, mammary, and ovarian tissues. Previously, all metastatic ovarian cancers were defined as Krukenberg tumor. In this case report we discuss the maternal death that occurred in a pregnancy in the third trimester in a pregnant woman with a severe form of COVID-19 disease and a metastatic ovarian cancer of a malignant pancreatic neuroendocrine tumor.

2. Introduction

The new coronavirus (SARS-CoV-2) is a single-stranded encapsulated RNA virus [1]. Immunologically, the human body's response to SARS-CoV-2 infection is based on the existence of an integral functional immune system [1]. COVID-19 disease can lead to a mild form, in which the virus is effectively eliminated by the immune system or a severe form, with a high mortality rate [1]. The positioning of the pregnant and post-pregnant human body on this prognostic-evolutionary scale appears to be unclear. The intra-gestational immune system adapts to allow the growth of a semiallogenous fetus [2], resulting in a modified immune response to infections during a gestation [3, 4]. Consequently, in order to understand SARS-CoV-2 infection during pregnancy, it is important to understand the pathophysiology and molecular mechanisms and to analyze them in the context of the modulated pregnant immune response.

Cytological, neuroendocrine cells are a series of nerve cells that react to signals from other nerve cells by releasing hormones into the blood. Topographically, these neuroendocrine cells are distributed throughout the human body and can suffer a series of malignant degenerations that generate neuroendocrine neoplasms.

3. Case Report

A 26-year-old patient, pregnant in week 29, was admitted with dyspnea and affirmatively cough with hemoptysis sputum. Objective good general health, skin and mucous pale, murmur vesicular present bilaterally hardened with crackles bilaterally, saturation of the oxygen = 92% in the ambient air, rhythmic cardiac beats without detectable gross flaws, abdomen increased in volume on account of pregnancy, Giordano negative, bilateral, ROT present. Biological inflammatory syndrome, hypokalemia, hyponatremia and anemic syndrome. The patient refuses to perform chest CT. Antiviral, analgesic and vitamin treatment is instituted.

After 48 h hospitalization the patient present desaturation: oxygen saturation 88% in ambient air followed by 95% extra oxygen by the nasal cannula 6 L/min and supplemented regimen Dexamethasone 2 x 4 mg/day. In spite of treatment shows a sudden desaturation with sat O^2 = 70% with supplemented oxygen 6 L/min, administer HHC 100 mg, bronchodilators and continue with supplemented oxygen 15 L/min with tank mask but Sat O^2 = 80-82% reason requests an UCI consultation following which the transfer to the UCI COVID-19 department was indicated.

On the UCI COVID-19 department, for ARDS it was decided to perform an emergency C-section, resulting in a live male fetus, 1,900 grams, followed by bilateral ovaria's tumors excision.

Surgery procedure: C-section, followed by a bilateral salpingoophorectomy.

The pathology exam after the surgery:

Macroscopic exam:

The 1st ovary and fallopian tube: tumor ovary of 11/10/6 cm with the capsule integrates and bumpy appearance and the fallopian tube attaches to the surface of the ovarian capsule. Section on the solid tumor: white-yellow and horn with whitish nodules.

The 2nd ovary and fallopian tube: tumor ovary 10/7 / 4.5 cm, with a bumpy, solid appearance, with an integral capsule. Horn 2 - 5 cm, attached to the surface of the ovary. On the ovary section the same solid, nodular tumor aspect.

The placenta approximately 14/9 cm, on sections with whitish streaks and umbilical cord approximately.

Microscopic exam:

Both tumor-transformed ovaries, examined in multiple sections, show the same histological aspect of a malignant proliferation of epithelial nature, consisting of well-differentiated tubulo-glandular pattern structures and relatively monotonous gastric-like columnar cell trabeculae, with intraluminal eosinophilic secretions, tumor necrosis and angioinvasion present. Mitotic index between 5-15 mitoses / mm^2. The stroma is fine, only focal in the necrotic areas is dense, collagenous. The capsule is not perforated.

Both fallopian tubes are non-tumorous.

The Ihc reactions were performed on ovarian tumors with the following profile:

- CK7, CK20, ER, HER2, WT1: negative
- CDX2: positive
- Chromogranin, synaptophysin, intensely positive CD56, diffuse tumor.
- Gal3 uninterpretable.

Placenta with villous and small foci deposits of perilous fibrin and foci of corangiosis, placental micro calcifications are present. Focal villous stromal edema present. Free membranes without modifications. Umbilical cord with 3 vessels in Warithon gelatin with loose appearance, edematous.

4. Conclusion

Bilateral ovarian metastases of neuroendocrine carcinoma of digestive origin.

After the surgery is carried out a chest CT which show a COVID-19 severe viral pneumonia, and the CT reported further aspect of unfavorable evolution by subcutaneous emphysema, pneumomediastin, pneumoperitoneum, bilateral solid PNO, despite the treatments administered on COVID UCI department (drugs, CPAP-BIPAP, IOT with VM, plasma, CER and ECMO).

The patient presents on 20.09. at 22.40 cardiac arrest by asystole resuscitation maneuvers begin, and at 23.50 death was declared:

Severe form COVID-19 pneumonia with consolidation.

Cardiac arrest by asystole.

ARDS.

Drained bilateral pneumothorax.

Severe sepsis.

Pluriorganic insufficiency.

Ovarian neuroendocrine tumors with digestive starting point with, hepatic, pancreatic splenic (possibly lung) metastases.

Postpartum 3-st week.

Emergency cesarean section with annexectomy.

4.1. Tomographic aspects

4.1.1. Native chest CT 04.09:

Multiple areas of extensive matte glass occupy almost all of the lung fields with sparing of the bilateral apical region, with a tendency to condensation, with thickening of the inter- and intra- lobular septa. Slight thickening of the right posterior pleura. No mediastinal lymphadenopathy or pulmonary hilum with pathological dimensions. On CT sections native upper abdomen, liver, pancreas, spleen, kidney normal limits. Conclusions: Imaging changes frequently associated with severe COVID-19 pneumonia.

4.1.2. CT chest native control 05.09:

Compared to the previous examination on 04.09. Unfavorable

evolutionary imaging aspect through: Bilateral cervical massive lateral subcutaneous emphysema supra and subclavicular bilateral, latero-thoracic, latero-abdominal

4.1.3. CT neck, native chest 07.09:

Subcutaneous emphysema in the soft parts of the neck and anterior thorax. Extensive condensation multiplexing with areas of frosted glass in both lung fields. Pneumomediastin. Pneumothorax. On CT section native upper abdomen: Normal-sized liver with more native hypodense lesions (cysts?). Gallbladder pancreas, spleen, kidneys, adrenal glands within normal limits. Conclusions: Aspect pulmonary CT of severe viral pneumonia. Subcutaneous emphysema. Pneumothorax. Mediastinal pneumonia.

4.1.4. CT 08.09:

Subcutaneous cervical and thoracic emphysema slightly reduced both quantitatively and as an extension. Bilateral pneumothorax much reduced in size-apical left blade 3 cm thick, anteriorly as a fine blade of maximum 0.5 cm at the pleural mediastinal retrosternal-air blade of about 3-3.5 cm extends and stylizes the heart.

4.1.5. Pathology

Death diagnostic:

Interstitial pneumonia with SARS-CoV-2. Adenocarcinoma pancreas. Postpartum. Septic spleen.

Lung: vascular thrombosis, ruptured alveolar septa, scaly pneumocytes, inflammatory cells, leukocyte alveolitis, abscessed areas, areas of hemorrhagic infarction. Abscessed bronchopneumonia with extensive areas of infarction.

Liver: dystrophic liver with an extensive area of necrosis, with a nodular tumor area, with the disposition of micro papillary tumor cells, solid areas, pseudo glandular. Small and or cylindrical tumor cells with monoform structure, tachychromatic nuclei, slightly granular eosinophilic cytoplasm, area, fibrous stroma, rare mitosis.

Heart: interstitial edema, some muscle fibers without nuclei.

Pancreas: extended necrosis and a tumor infiltrated area with carcinoma structure with acinar cell disposition, differentiated tubular structures.

Uterus: wall with muscle fibers, necrosis, thrombosis, area of hemorrhagic infarction.

Ovaries: described above.

Kidneys: necrosis of the urinary tract epithelium, in some places, complete necrosis.

Diagnosis:

Carcinoma tumor in the liver and pancreas.

Abscessed bronchopneumonia.

Extensive areas of hemorrhagic infarction.

Correlating with the antecedents, with the surgery in which the metastatic neuroendocrine ovarian tumor (HE and IHC staining) was diagnosed.

Tumors detected on the liver and pancreas (HE staining) are structurally included in neuroendocrine carcinomas, possibly primary, in one of these organs.

According to literature, primary ovarian endocrine tumors are rare, usually associated with a teratoma.

The presence of tumors in the liver and pancreas pleads for the primary neuroendocrine tumor in the digestive tract (metastases of ovarian neuendocrine tumor originate in 67% of cases in the ileum, pancreas, appendix).

Final diagnosis correlated with the described data:

Pancreatic malignant neuroendocrine tumor with liver and ovarian metastases.

5. Discussion

Pathologically, neuroendocrine neoplasms are generally defined as epithelial neoplasms with the predominant presence of neuroendocrine cells distributed individually or in small nests (of neuroendocrine differentiation) [5]. Generically, many neuroendocrine neoplasms have been classically referred to as "carcinoids", but this name does not accurately explain their variable biology, histological differentiation and their secretory potential [6].

The term "neuroendocrine malignancy" is used to refer to the group of solid malignancies that are thought to originate from neuroendocrine cells throughout the human body, including "carcinoid tumors". Neuroendocrine neoplasms occur in a variety of anatomical: pulmonary, gastric, intestinal (thin), pancreatic, recto-colic, mammary, and ovarian sites.

Most neuroendocrine tumors occur in the gastrointestinal tract (67.5%) and the bronchopulmonary tract (25.3%) [7]. In the gastrointestinal tract, most neuroendocrine tumors occur in the small intestine (41.8%), rectum (27, 4%) and stomach (8.7%) and less than 1% of neuroendocrine neoplasms occur in the pancreas [8]. Other anatomical locations where neuroendocrine neoplasms occur, but very rarely, include the uterus, ovary, breast and larynx [9].

SARS-CoV-2 binds to the conversion enzyme angiotensin-2 (ACE2), a cell surface receptor, and a potential interaction has been reported between SARS-CoV-2 and the renin-angiotensin-aldosterone system [10, 11, 12, 13]. However, such interactions between SARS-CoV-2 or other viruses and SARS receptors expressed on neuroendocrine neoplasms (NEN), such as somatostatin receptors (SSRs) and histamine receptors (H1 and H2 receptors), have not been reported.

Please note that to date, the specific effects of SARS-C-oV-2 infection in patients with NEN have not yet been reported.

Statistically, neuroendocrine neoplasms (NEN) are rare neoplasms that occur in cells of the diffuse endocrine system, scattered mainly in the digestive system and respiratory tract. Most NENs evolve slowly and the charges and signs may be related to tumor formation (dysfunctional, NF-NEN) and / or hormonal hypersecretion

(functional, F-NEN). Pathologically, most NENs are well-differentiated tumors (WD) of grade 1 (G1, Ki67 ≤2%), grade 2 (G2, Ki67 3-20%) or grade 3 (G3, Ki67> 20%), while they are small fraction are defined as small cell or large cell neuroendocrine carcinoma (NEC) poorly differentiated (NEC) with a Ki67> 20% [14, 15].

Patients with NEN and severe infections that cause difficulty breathing or gastrointestinal (GI) symptoms (eg diarrhea, nausea and vomiting) should be hospitalized. Some pregnant women with Covid-19 disease may have an undiagnosed underlying NEN and this possibility should be considered in those people whose symptoms, such as diarrhea or wheezing with difficulty breathing, do not resolve or whose symptoms have been chronic.

We consider that this case has some features and gives rise to a number of questions to which we can answer only partially.

5.1. Particularities

In our opinion the first particularity of this clinical case lies in the fact that, at a previous hospitalization, at the beginning of the second trimester of pregnancy, at 15-16 weeks gestation age, the pregnant woman was recommended to perform immediate surgical tumor excision, but she refused, on his own responsibility against medical advice.

The second particularity of the case was that even if we could not annihilate the thanatogenic effect of the infection in the mother, the newborn did not present COVID-19, i.e. there was no vertical viral transmission mother-fetus, and the newborn showed a favorable evolution, corresponding to the degree of prematurity.

The third particularity lies in the poverty of similar data in the literature

5.2. Questions waiting to be answered

Despite our best knowledges and efforts in this case, we cannot answer completely the following obstetric and bioethical questions with demonstrable certainty:

- *What evolution would have been the case if the pregnant woman accepted the tumor excision for the first time?*

Hard to respond pertinently, due to the increased risk of triggering the birth of an IVth degree premature post-tumor excision surgery, performed at 15-16 weeks gestational age, which may not be recoverable. We mention that the postpartum newborn at 29 weeks of gestational age had an evolution corresponding to the degree of prematurity. However, the patient refused the surgery.

- *What would have been the pregnancy and the fetus prognostic if the patient had not contracted SARS-CoV-2 infection?*

Certainly, under pertinent clinical and paraclinical monitoring, the pregnancy could have reached preterm or even term, when it would have been born by C-section and the ovarian tumors could have been surgically removed.

- *What evolution would the pregnancy have had if the patient had validated the asymptomatic form of the disease?*

Unpredictable, either without major effect on the pregnant woman or the newborn, or with a severe evolution with effects on the pregnant woman and the newborn.

- *How much did COVID-19 matter in the fatal outcome?*

A lot, because it triggered, maintained and aggravated ARDS and multiorgan failure.

- *Could the pregnant woman be saved, when and how?*

Maybe, but not sure, if the obstetric-surgical intervention would have taken place with 12-48 hours earlier.

6. Conclusions

- The severe form of SARS-CoV-2 infection triggers a pluriorganic pathophysiologic degradation with remarkable tanatogenic potential.
- We do not have an effective anti-COVID-19 curative panacea that saves lives.
- We do not have sufficient data on the prevalence, clinical picture and possible complications of SARS-CoV-2 infection intra and post-gestation in NEN metastatic ovarian cancer.
- NEN coexistence has a negative influence on the course of COVID-19 disease in pregnant women.
- Future studies on similar cases are needed in order to be able to pertinently answer to questions raised in our case report.

References

1. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). 2021.
2. John E, Jorge M, Jonathan W, Vicki L, Smith R. Mechanisms of maternal immune tolerance during pregnancy. In: Recent Advances in Research on the Human Placenta, edited by Zhang J. London: InTech, 2012.
3. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis. 2006; 12: 1638-43.
4. Silasi M, Cardenas I, Kwon JY, Racicot K, Aldo P, Mor G. Viral infections during pregnancy. Am J Reprod Immunol. 2015; 73: 199-213.
5. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) is based on the World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9). ICD-9-CM is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.
6. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading and staging systems. Pancreas. 2012; 39: 707-12.

7. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, mares JE et al. One hundred years after 'carcinoid:' epidemiology of and prognostic factors for neuroendocrine tumours in 35,825 cases in the United States. J Clin Oncol. 2008; 26: 3063-72.

8. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumours. Cancer. 2003; 97: 943-59.

9. Modlin IM, Shapiro MD, Kidd M. An analysis of rare carcinoid tumors: clarifying these clinical conundrums. World J Surg. 2005; 29: 92-101.

10. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. New England Journal of Medicine. 2020; 382: 1653-9.

11. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003; 426: 450-4.

12. Hoffmann M, KleineWeber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 18: 271-80.

13. Li W, Zhang C, Sui J, Kuhn JH, Moore MJ, Luo S, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J. 2005; 24: 1634-43.

14. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017; 3: 1335-42.

15. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol. 2018; 31: 1770-86.