



Salivary gland carcinoma with distant metastases and pregnancy – multidisciplinary challenges

Sigutė Miškinytė¹, Ieva Bartuševičienė^{1,2}, Guoda Žukienė^{1,3}, Dalia Laužikienė^{1,3}, Diana Ramašauskaitė^{1,3}, Jūratė Šipylaitė^{1,2}, Diana Gasiūnaitė^{1,2}

¹Vilnius University, Faculty of Medicine, Vilnius, Lithuania

²Vilnius University Hospital Santaros Clinics, Center of Anesthesia, Intensive Care and Pain Management, Vilnius, Lithuania

³Vilnius University Hospital Santaros Clinics, Center of Obstetrics and Gynecology, Vilnius, Lithuania

Abstract

Background. Although salivary gland cancer is rare, its rapid progression during pregnancy is reported in literature and presents complex challenges to the medical team. In this article we describe the challenges that the multidisciplinary team faced, in detail describing an anticipated complicated anesthesia during the Cesarean section due to the advanced liver disease and difficult airways after cancer removal surgery.

Case report. A 35 year old female patient was diagnosed with adenoidal cystic salivary gland carcinoma with distant metastases. Surgery was performed to remove the primary tumor and the metastases, chemotherapy, and an anti-cancer medication Lenvatinib were used to treat the remaining metastases. The patient then presented to the emergency room at 26 weeks pregnant with complaints related to the rapidly progressing oncological disease and metastases in the liver. She was hospitalized, treated with Lenvatinib, betamethasone to prevent newborn respiratory distress syndrome and a Cesarean section was planned to be performed at 32 weeks of pregnancy to save the patient's life.

Conclusions. Pregnant patients with malignant tumors need multidisciplinary care and management, as well as individualized decision making about the pregnancy, delivery and the treatment of cancer along with the management of the consequences.

Keywords: salivary gland carcinoma, pregnancy, multidisciplinary team, difficult airways.

Introduction

Cancer complicates approximately 1:1000 pregnancies with an increased rate in older age (1). Salivary gland cancer is rare, with an incidence of 1.3:100 000 per year (2). The coincidence of salivary gland cancer with pregnancy is even more rare, with only a handful of cases reported internationally (3, 4, 5). Rapid progression of a previously stable salivary gland mass in pregnancy is a common feature of these cases, suggesting an etiological link and encouraging scientists to investigate possible pathophysiological mechanisms (3, 6). Cancer in pregnancy presents complex medical, ethical and psychological challenges and should be managed by a multidisciplinary team, as both the prognosis of the mother and the fetus may be compromised (7). In this article we would like to present a clinical case (managed by a multidisciplinary team of doctors from the departments of Obstetrics and Gynecology, Oncology, Anesthesiology and Intensive Care) of a rapidly progressing salivary gland carcinoma in pregnancy as well as review the literature on this topic.

Case report

A 35 year old female patient was diagnosed with adenoidal cystic salivary gland carcinoma with distant metastases in the liver and in the lungs (stage IV – cT2N1M1) in October 2019. In the years 2019 - 2020 she had a surgery of the maxilla and the palate to remove the primary tumor as well as transarterial chemoembolization of the tumor. A right hemihepatectomy was

performed due to the distant metastases (75% of the liver was removed). In 2021 metastases were found in the remaining liver and the patient was treated with three cycles of chemotherapy (no data about a specific chemotherapy drug was found in the patient's medical charts). Following this treatment Lenvatinib (an anti-cancer medication and kinase (which are important in cancer pathogenesis) inhibitor) was suggested to the patient. She was taking Lenvatinib for around 6 months and felt a clinical improvement but the patient discontinued the treatment 8 months ago. The last CT (computer tomography) scan was performed in December 2021, there were no changes in the mouth and pharynx as well as no new masses in the liver, although some of the previously found masses were enlarged.

The patient presented to the emergency department at 26 weeks pregnant complaining of acute abdominal pain (mainly in the epigastric region) with difficulty breathing, nausea and vomiting. On clinical examination a painful and hypertrophic left lobe of the liver was palpated. An abdominal ultrasound in the emergency department revealed metastasis-like hepatic lesions, splenomegaly and free fluid in the abdomen. The patient's laboratory values in the emergency department are presented in Table 1, the patient presented with a low hemoglobin, creatinine and albumin and high fibrinogen and bilirubin.

This was a second pregnancy for this patient, she had a termination of the first pregnancy due to conception during chemotherapy.

Table 1. The patient's laboratory values during pregnancy

Laboratory values	At 26 weeks of pregnancy (at the emergency department)	At 30 weeks of pregnancy (on the day of the surgery)	Normal ranges
Leukocytes ($\times 10^9/L$)	5,98	9,07	4,0 – 9,8
Thrombocytes ($\times 10^9/L$)	140	157	140 - 450
Hemoglobin (g/L)	96	97	117-145
Urea (mmol/L)	2,7	3,0	2,5 – 7,5
Creatinine (mcmol/L)	35	30	49 - 90
Bilirubin (total) (mcmol/L)	47,9	43,6	< 21
Bilirubin (unconjugated) (mcmol/L)	17,2	28,5	< 15,7
ASAT (U/L)	24	39	≤ 40
ALAT (U/L)	12	41	≤ 40
Albumin (g/L)	25,2	29,3	35 - 52
ADTL (s)	40,2	38,8	28-40
Prothrombin complex activity SPA (%)	106	96	70 - 130
SPA (INR)	0.98	1,02	0,9 – 1,19
Fibrinogen (g/L)	5,18	5,55	2 - 4
Na (mmol/L)	134	131	134 - 145
K (mmol/L)	3,8	4,6	3,5 – 5,0
Cl (mmol/L)	102	103	98 - 107

This pregnancy was confirmed at 6 weeks, the patient refused termination which was needed to start chemotherapy as the disease was rapidly progressing. At 13 weeks a medical geneticist consulted the patient, no fetal developmental abnormalities or markers of chromosomal diseases were found. At 18 weeks the fetal physical development corresponded with the 18 weeks of pregnancy.

Having excluded acute surgical pathologies a multidisciplinary team decided to hospitalize the patient, start the treatment with betamethasone for fetal lung maturation and targeted therapy with Lenvatinib, as well as to perform a Cesarean section at 32 weeks of pregnancy.

The patient received betamethasone but refused targeted therapy. The multidisciplinary team (consisting of doctors from the departments of

Obstetrics and Gynecology, Oncology, Abdominal Surgery, Anesthesia and Intensive Care) concluded that the patient should then receive Lenvatinib as a life-saving measure even though no data on the effects for the fetus was available. The delivery was planned at 32 weeks of pregnancy via Cesarean section, spinal anesthesia was set to be performed.

On preoperative evaluation the anesthesiologist found that the patient had restricted mouth opening (maximum 1.5 cm) due to the resection of the primary tumor. The patient was categorized as Mallampati IV with difficult airways as tracheal intubation with a laryngoscope was impossible. During the pregnancy the patient had episodes of thrombocytopenia (lowest count 50×10^9) and, likely, coagulopathy due to a small and metastatic remaining part of the liver and progressing liver failure. Combining that with the possibility of insufficient spinal anesthesia or other unanticipated circumstances, the preparation for general anesthesia was considered. An otorhinolaryngologist consulted the patient and concluded that fibrobronchoscopy intubation would be possible if needed.

Due to the worsening condition of the patient (severe fatigue, headaches, severe pain in the epigastric and sternal areas) the Cesarean section was performed at 30 weeks of pregnancy. The patient's laboratory values on the day of the Cesarean section (at 30 weeks pregnant) are presented in Table 1, the changes in laboratory values were the similar as in the emergency department (anemia, hyperbilirubinemia, hypoalbuminemia).

At 26 weeks of pregnancy the patient received a lower dose spinal anesthesia in a lying on the

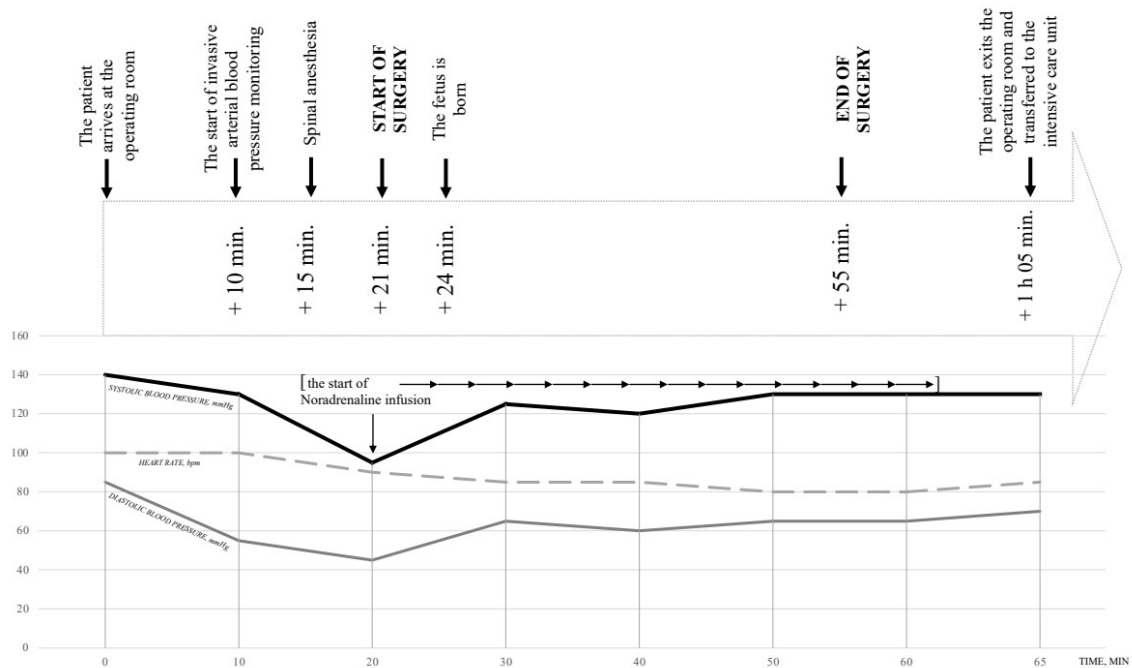
right side position (height of the patient - 159 cm; 10 mg of 0.5% hyperbaric bupivacaine + 10 mcg of 0.005% fentanyl were injected intrathecally into the L3 - L4 spinal space), opioid analgesics and intravenous propofol were given for additional pain management as well as 5 L/min of O₂ through a face mask. The patient was breathing spontaneously through the whole surgery, no additional techniques of airway management were used. Before spinal anesthesia two peripheral vein catheters were placed and invasive arterial blood pressure monitoring was started. After the delivery the patient became hemodynamically unstable, noradrenaline with a maximum dose of 0.1 mcg/kg/min was used in order to maintain mean arterial pressure ≥ 65 mmHg. The need for vasopressors resolved until the end of the surgery. The surgery and anesthesia both went according to the preconceived plan. The patient's vital parameters and interventions during the surgery can be seen in Figure 1. For further monitoring, treatment and care the patient was transferred to the Intensive Care Department for 24 hours (2 units of red blood cells were transfused; the patient was provided analgesia with NSAIDs (non-steroidal anti-inflammatory drugs) and opioid analgesics as well as prophylaxis with LMWH (low molecular weight heparin) for DVT (deep vein thrombosis) prophylaxis. After 24 hours the patient was transferred to the Department of Obstetrics to further plan the cancer treatment in accordance with an oncologist.

A male 1460 g and 44 cm newborn was born via the Cesarean section at 30 gestational weeks. The newborn was evaluated as Apgar 8/8 and transferred to the Neonatal Intensive Care Unit

for further treatment due to respiratory failure

caused by the premature birth.

Figure 1. The patient's vital parameters and interventions used in the operating room.



Literature review and discussion

In the last twenty years cancer treatment has developed extensively, leading to better outcomes for oncological patients. Cancer during pregnancy occurs in 140 per 100 000 pregnancies (8). It has been noted that this rate is increasing because women nowadays prefer to delay giving birth to a later age. Cancer treatment for pregnant women should follow standardized protocols as much as possible. In majority of the cases surgery to remove or reduce cancer is possible, regardless of gestational age. Radiotherapy should be considered cautiously as the effect to the fetus depends on the given dose of radiation, treatment field and gestational age. Given the fact that most chemotherapeutical agents easily cross the placental barrier, this treatment is not

recommended before the 12th week of pregnancy in order to prevent the risks of congenital defects (9). In the past decade immunotherapy has become available but up until now the data is sparse on how these immunotherapy agents may affect fertility, pregnancy and the fetus. The little available evidence on targeted and hormonal therapies has demonstrated that most agents are contraindicated for pregnant women. It is commonly advised to suspend this treatment until after the delivery with the only exception for imatinib and rituximab, which can be safely used after the 12th week of pregnancy (10). The association between pregnancy and growth of salivary gland malignancies has not been well elucidated due to the paucity of reports in the literature (11). However, adenoid cystic

carcinoma of the salivary glands is known to share histologic characteristics (positive estrogen and progesterone receptor expression) with adenocarcinomas of the breast (12). While the role of pregnancy related hormones on growth of salivary gland malignancies has to be further investigated, there is some evidence that estrogen, progesterone or other pregnancy related hormones may play a role (13). The rapid progression of the carcinoma in pregnancy was also seen in our clinical case. Although we cannot conclude that the progression was specifically due to pregnancy and pregnancy related hormones since the patient did not receive full treatment and check-ups even before the pregnancy, we know that the clinical symptoms related to the carcinoma progression appeared only in pregnancy (at 5 weeks). Because of the rapid progression of the disease the patient was discussed in a multidisciplinary team. The team decided to treat the patient with Lenvatinib - an anti-cancer medication kinase (which are important in cancer pathogenesis) inhibitor as the patient reported clinical improvement when using this drug before pregnancy. There is no data on the effect for the fetus, but in earlier studies with animals Lenvatinib resulted in embryotoxicity, fetotoxicity, and teratogenicity when administered to rabbits and rats at doses below the recommended human dose (based on body surface area) (14). For this reason, this agent should be avoided in pregnancy unless necessary and after a precise consideration of the benefits or needs to pregnant women and the potential risk to the fetus. However, as the patient was refusing targeted therapy it was considered a life-saving medication and was prescribed for the last month of the pregnancy before the Cesarean section.

The primary tumor resection presented additional challenges in this clinical case, as the consequences of maxillary surgery are always related to structural changes in the upper airways. Surgical resection of cancer in the soft palate is usually reconstructed by soft tissue transplantation. The structural abnormalities after the reconstruction represent a challenge in airway management - the patients after soft palate cancer resection with reconstruction are usually easy to ventilate but difficult to intubate (15). Consequently, various guidelines on anticipated difficult airways describe the advantage of using a video laryngoscope (16, 17). However, in many cases the patients have a restricted mouth opening, so the use of a video laryngoscope may be limited. A nasotracheal intubation could then be considered, but in some patients, it can be unsuccessful because of the aforementioned structural changes after surgery (the reconstructed tissues might be teared). In our described situation a nasotracheal intubation was also considered but unprioritized because of the aforementioned soft tissue tear risk due to palatine structural defects after surgery. Considering previous points, fibrobronchoscopy intubation could be the gold standard in these situations and it was considered in our clinical case when preparing for possible general anesthesia and anticipating difficult intubation because of the patient's restricted mouth opening. An otorhinolaryngologist consulted the patient before the Cesarean section and concluded that fibrobronchoscopy intubation is possible in this case. The progression of liver failure (25% of the hepatic tissue was left with growing metastatic masses) which could result in changes in

coagulation and the history of thrombocytopenia during pregnancy also increased the possibility of having to use general anesthesia. Although coagulopathy should be considered as a contraindication to spinal anesthesia, this method of anesthesia is increasingly performed in thrombocytopenic patients at the time of delivery of pregnancy (18, 19). There is a lack of data regarding the optimum platelet count at which spinal procedures can be safely performed as reports are often confounded by the presence of other risk factors such as anticoagulants, antiplatelet agents and other acquired or congenital coagulopathies/platelet function defects or rapidly falling platelet counts. In the absence of these additional risk factors, a platelet count of 80×10^9 is considered safe for performing epidural or spinal anesthesia (19). In our clinical case the patient had episodes of thrombocytopenia during pregnancy (lowest count was 50×10^9) but the thrombocyte count was normal at the time of delivery (157×10^9) so the spinal anesthesia was performed safely. The patient also received a lower dose spinal anesthesia using hyperbaric 0.5% bupivacaine to minimize the cardiovascular and respiratory systemic effects. Spinal anesthesia was preferred over epidural not only for its rapid onset and adequate motor blockade but also because of the high failure rate of epidural anesthesia in scheduled Cesarean sections, and the reported need for additional sedatives and a longer time spent in the operating room (20, 21). The possibility of unstable hemodynamics in the operating room was anticipated due to the patient having a severe overall condition due to cancer, relative hypovolemia due to hypoalbuminemia

and ascites, therefore the patient had invasive arterial blood pressure monitoring, two peripheral intravenous catheters and noradrenaline infusion was ready if needed during the Cesarean section. Although we found a case in literature of salivary gland carcinoma in pregnancy in which epidural anesthesia was used during the Cesarean section, we chose spinal anesthesia for this patient having in mind the risk of arterial blood pressure falling or insufficient spinal block as we could manage the arterial blood pressure with vasopressors and in case of the insufficient spinal block add intravenous analgesics, which was successfully done during the Cesarean section (6).

Conclusions

Pregnant patients with malignant tumors need multidisciplinary care and management, as well as individualized decision making about the pregnancy, delivery, and the treatment of cancer along with the management of the consequences.

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