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REVIEW ARTICLE

The effect of cannabis in the treatment of Hodgkin's lymphoma in a pregnant patient - extensive case report and literature review

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Summary

Purpose: *Hodgkin lymphoma (HL) is the fourth most frequent cancer diagnosis among pregnant females. A multidisciplinary team is mandatory to obtain the best treatment and prognosis for the mother and for the baby. Here, we present the case of a patient diagnosed with HL and its evolution during 2 pregnancies.*

Case presentation: *Herein we present the case of a 21-year-old female Caucasian patient, with free history, diagnosed with HL stage IIB. The patient started first line chemotherapy and radiotherapy, with incomplete remission. She refused any other treatment. Five years later, the patient became pregnant and was offered chemotherapy in the 2nd trimester of pregnancy, that she refused, and delivered by C-section at 37 weeks. In the same year, the patient became pregnant again and was proposed termination of pregnancy, that she also refused. The MRI scan revealed progression of HL and she was admitted in the hospital several times for altered general condition, respiratory infections and increased need of painkillers including opioids. At 26 weeks of pregnancy, the patient began on her own a treatment with pure cannabis. Her pain and general status got better and the tumor tissue decreased. She delivered by C-section at 34 weeks a boy that presented in the first 24 h postpartum a withdrawal syndrome and intestinal invagination, requiring care in NICU and surgery with bowel resection.*

Conclusion: *Therefore, we can conclude that cannabis could be part of oncological treatment. No other case like this, as far as we know, has been previously reported.*

Key words: *Hodgkin lymphoma, Δ^9-tetrahydrocannabinol, pregnancy*

Introduction

Hodgkin lymphoma (HL) is the fourth most frequent malignancy diagnosed among pregnant females after melanoma, breast and cervical cancer [1] with an estimated prevalence of 1:6000 pregnancies. If diagnosed and treated early, HL is one of the most curable forms of cancer, even in late stages [2]. A multidisciplinary team is mandatory to obtain the best treatment and prognosis for the mother and for the newborn.

Recent studies have demonstrated that cannabinoids also have anticancer activity and as cannabinoids are usually well tolerated and do not produce the typical toxic effects of conventional chemotherapies, there is considerable merit in the development of cannabinoids as potential anticancer therapies [3].

Pregnancy limits the management of HL. Chemotherapy is most likely safe in the second half of the pregnancy. Treatment decisions are made based on clinical presentation, drug interactions with pregnancy, and the effects of such treatment on fetuses and newborns [1].

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There are many studies on pregnant patients diagnosed with HL that have been treated with ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), but few studies on treatment with THC (Δ^9-tetrahydrocannabinol) on HL in women that are not pregnant [4], and no reported cases as far as we know about treatment for HL in pregnant patients. The purpose of this review article was to highlight the importance of THC as a novel anticancer agent useful even in pregnant patients, starting from the case of a patient diagnosed with HL and its evolution during 2 pregnancies, having been under only a self-induced cannabinoid treatment, refusing chemotherapy.

Case presentation

We present the case of a 21-year-old Romanian female patient,with no obstetrical history diagnosed in 2009 with HL stage IIB, for which she started first line chemotherapy with ABVD for 6 months that she tolerated poorly. The therapy was completed with radiotherapy in 20 sessions with 20Gy. Under this treatment the disease was in incomplete remission, with the persistence of a thoracic lymphoma tissue about 2 cm in diameter. She refused any other treatment and left without any follow-up.

In 2014 the patient became pregnant and was referred to our service at 7 weeks of amenorrhea. The evolution of the pregnancy was physiological, with normal screening test results at 12 weeks. The progressive aspect of the malignancy was taken into consideration, so an MRI scan was scheduled at 14 weeks of amenorrhea that revealed a HL with left lung involvement, posterior and anterior mediastinal extension with anterior right pleural-pulmonary determination and extension to the anterior right ribs (Figure 1).

In the following month, a tumor of approximately 15/13 cm located at the level of the right superior hemi-thorax appeared, a biopsy was taken, and the pathology result confirmed yet again HL. A multidisciplinary team was formed by an obstetrician, an oncologist and a surgeon, and the indication of chemotherapy was set, but the patient refused.

During pregnancy she had repeated episodes of respiratory infections with dyspnea and low O_2 saturation, but from an obstetrical point of view, the development of the pregnancy was normal (Figure 2) and a male child was born by caesarean section at 37 weeks, weighing 2500 grams, Apgar score 10.

In the same year, 2015, the patient became pregnant again, while still breastfeeding the first child. The multidisciplinary team recommended the termination of the pregnancy due to vital maternal risk, but the patient refused. The disease progressed further, with numerous complications: hemoptysis, dyspnea and terrible chest pain with an increased need for analgesic treatment: acetaminophen, codeine, tramadol and metamizole, administered iv at a 4-6 h time interval. The MRI scan revealed the progression of HL, chest bone involvement (ribs and clavicles) and bone marrow involvement (Figure 3).

By her own decision, at 26 weeks of pregnancy, the patient began topic cannabis oil application on

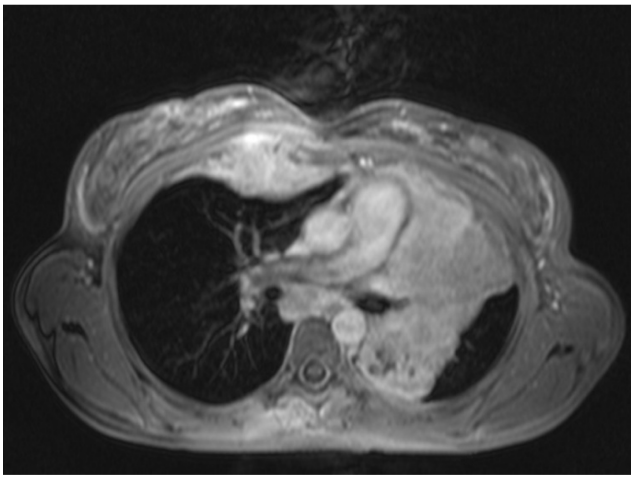

Figure 1. MRI at 14 weeks of amenorrhea of the 1st pregnancy showing HL with left lung involvement, mediastinal extension with right pleural-pulmonary determination and extension to the anterior right ribs.

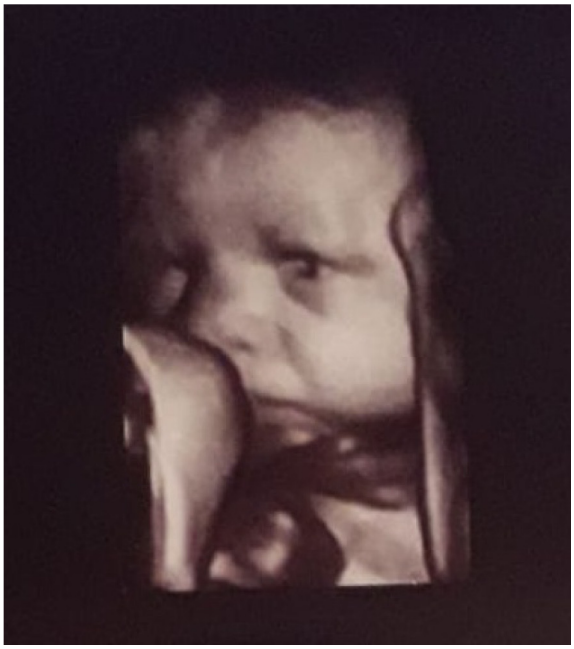

Figure 2. 3D Ultrasound image from the 1st baby showing 3d normal face with opened eye.

the supraclavicular tumor and an oral treatment with pure oil cannabis between 1 and 5 ml, 3 times per day. This significantly relieved pain, improved the quality of life and reduced the dimensions of the supraclavicular tumor at 8.3 cm. Her general status during the late 3rd trimester worsened with respiratory distress, being dependent on O_2 inhalation, but the fetus was developing normally (Figure 4), and at 34 weeks of gestation, she delivered by C-section a male baby, weighing 2380 grams, Apgar score 8/9.

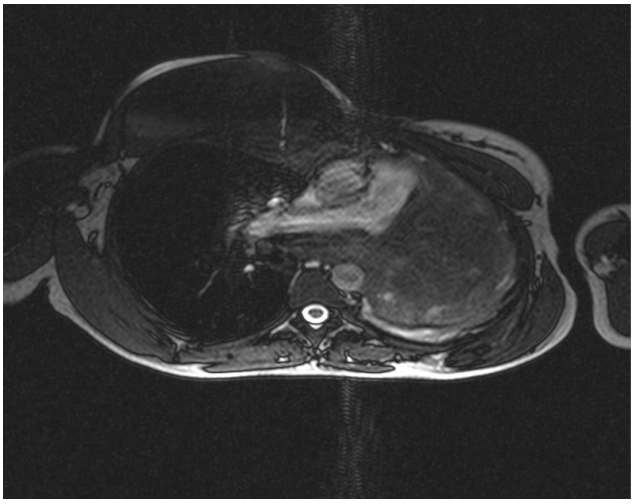

Figure 3. MRI Exam 2015 during 2nd pregnancy showing HL with complete left lung atelectasis, right rib and clavicle involvment and supraclavicular lesion.

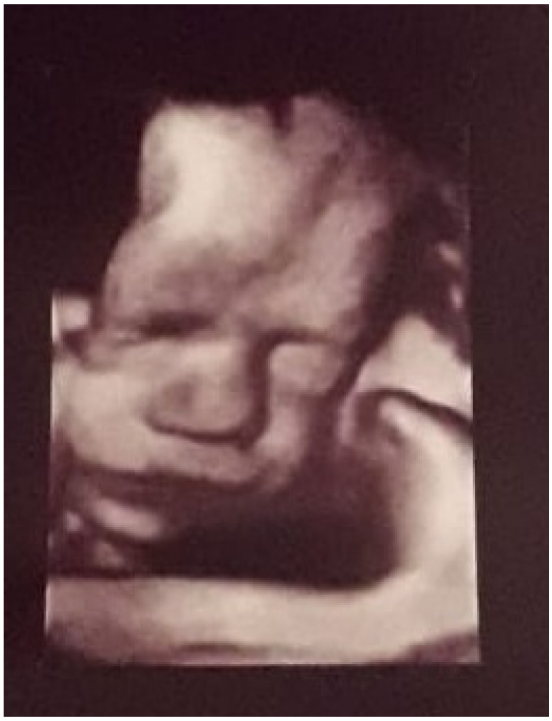

Figure 4. 3D Ultrasound Image of the 2nd baby showing 3D normal face.

During the first 24 h of life, the newborn developed withdrawal symptoms whose mother has been under treatment of cannabis and opioids derivatives, which is why he was administered morphine 0.1 mg every 6 h in NICU (neonatal intensive care unit).

The newborn baby presented in the second day of life acute surgical abdomen due to neonatal peritonitis, so he had emergency surgery in the Infant Surgery Department of Oradea. During surgery an invagination of the small bowel was discovered, for which a resection was done. Post-surgical recovery was favorable, the development of the child being normal for his age.

During the postpartum period, the mother's disease progressed, the patient was hospitalized in Madrid, restaged in HL stage IVB, with nodular sclerosis and left lung atelectasis, and started treatment with DHAP (dexamethasone, cytarabine, cisplatin) for only two cycles due to cardiotoxicity induced by cisplatin.

After a short period of time, immunotherapy (brentuximab vedotin) and chemotherapy using Gemcitabine and Vinorelbine followed by bone marrow autologous cell stem transplant (2016), but another cervical lymph node appeared, and was removed, reconfirming the presence of HL (2017). Until December 2019 she left oncological follow-up and currently MRI scans show complete left lung atelectasis, multiple nodular tumors of the right lung with lymphoma infiltration having both peritoneal and retroperitoneal carcinomatosis (Figure 5). She started a salvage regimen with Brentuximab in association with IGEV (Etoposide, Ifosfamide, Uromitexane, Carboplatin). Currently we cannot exclude that the patient remained a cannabis user.

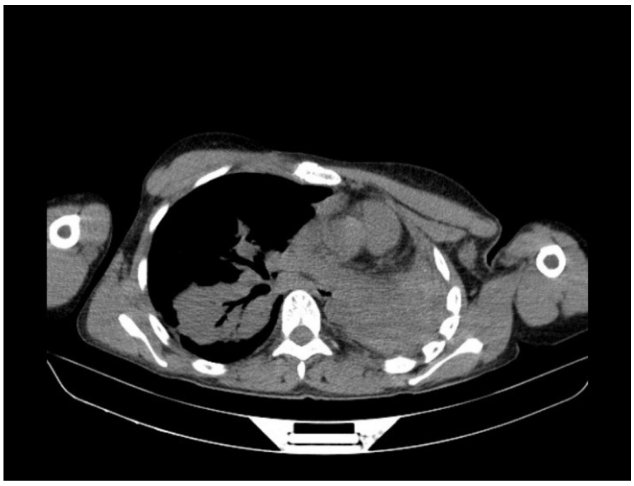

Figure 5. CT image in 2019 showing HL with complete left lung atelectasis and multiple nodular tumors of the right lung with lymphoma infiltration.

Discussion

The diagnosis and treatment of HL in pregnant women is very difficult because of the limits imposed by gestation. The objective of the treatment is to maximize the mother's prognosis, without impairing the fetus and newborn prognosis.

As other studies have shown, fertility is not affected after chemotherapy and women can get pregnant and deliver [5].

The characteristics of the disease are the same, no matter the presence of pregnancy, the clinical presentation and the histological types and stages of the disease rest unchanged. The guiding principle in pregnancy is to restrict radiologic staging to the minimum and to identify the disease that seriously threatens the immediate well-being of the mother or child. For this, computed tomography and positron emission tomography (PET) should be avoided, and use a simple anterior-posterior radiography of the chest with proper shielding, abdominal ultrasound for the extent of the disease and magnetic resonance imaging (MRI) after the first trimester for further detailed imaging [4-6].

Early studies in the 1950s suggest an association between pregnancy and disease progression, but most actual available evidence reveals that pregnancy itself does not affect the course of HL, the response to therapy or the overall survival rate [7], nor does becoming pregnant increases the chances of relapse for HL after the disease has been effectively treated.

The decision to initiate therapy during pregnancy is influenced by fetal, maternal and disease related factors. The most important factors are the trimester at which the diagnosis was established, the stage and aggressiveness of the disease and the presence of life threatening symptoms. Recent data suggest that the delay of therapy until the 2nd trimester is desirable, if this is considered will not compromise maternal outcome. For some patients, deferral of therapy to the postpartum period is considered feasible [8].

The decision to administer antenatal therapy is heavily influenced by the stage of development of the fetus and the fetal being, as well as the extent of mother's disease, which will influence the outcome if the decision is made to defer therapy. In general, if the patient chooses to keep the pregnancy, the initiation of treatment will be delayed until the second trimester, or, with close surveillance of slowly progressive HL diagnosed during the first trimester, treatment can often be delayed in many cases to the postpartum period. Patients with HL with extensive disease burden represent an increased therapeutic challenge, especially when are diagnosed in the 1st trimester of pregnancy when systemic therapy would be expected to pose a serious threat to the developing fetus and significant delay of therapy could have fatal consequences for the mother [9].

Cannabis sativa contains a number of chemical compounds which activate cannabinoid receptors in the brain. Two major types of cannabinoid receptors have been characterized: CB1 and CB2. CB1 receptors are found mainly in central and peripheral neurons, CB2 receptors are found most often in immune cells [10]. There are more than 60 cannabinoids in marijuana [9] with 2 particular subjects of most studies for medical delta-9-tetrahydrocannabinol and cannabidiol (CBD).

Δ^9-tetrahydrocannabinol, the principal biologically active component of marijuana and of the cannabinoid family, exerts the effects through cannabinoid receptors. These receptors also have an endogenous ligand known as arachidonoyl ethanolamine (anandamide) which is an endogenous cannabinoid [11]. THC is responsible for the feeling of "high", but it has also analgesic, antiemetic, anti-inflammatory and antioxidant properties [9]. CBD has anxiolytic, antipsychotic and anticonvulsive properties [12].

There are few studies on the treatment with THC on HL in women that are not pregnant, mainly in ameliorating chemotherapy-related adverse events, i.e. general well-being, appetite, and nausea and also in pain [3].

Cannabinoids affect many essential cellular processes and signaling pathways which are crucial for tumor development [13-15], as they can induce cell cycle arrest, promote apoptosis, and inhibit proliferation, migration and angiogenesis in tumor cells [14,15]. In this way we explain the macroscopic tumor reduction in this patient after starting oral medical cannabis.

It has been shown that cannabinoids (endo and exogenous) exert a clear direct effect in maintening the uterine quiescence during normal pregnancy [11]. It is also known that THC molecule crosses the placenta, being highly lipophilic and distributed rapidly to the brain and fat of the fetus after ingestion/inhalation in proportion that varies from one-third to one-tenth of maternal concentrations [16].

THC rapidly penetrates highly vascularized tissues including the liver, heart, fat, lung, jejunum, kidney, spleen, mammary gland, placenta, adrenal cortex, muscle, thyroid, and pituitary gland. It can be found in small amounts in breast milk [16].

Regarding the adverse effect of Δ^9-tetrahydrocannabinol on pregnancy and on the neonate, two systematic reviews of Gunn et al [17] and Conner

et al [18] have found a potential effect on uterine blood flow (increased placental resistance and reduced circulation) and a higher risk for maternal anemia and a slight decrease in birth weight, possibly needing admittance in Neonatal Intensive Care Unit, but no independent relationship between prenatal marijuana use and preterm birth, spontaneous abortions, pregnancy complications, Apgar Scores or physical anomalies.

Another study conducted by Dotter-Kratz et al [19] revealed data on 35 weeks preterm infants coming from mothers with prenatal exposure to marijuana and found out that THC had no detrimental effect on neonatal death, neonatal intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia or cerebral palsy.

Although there are many adverse effects of the newborn exposure to cannabis we did not find invagination being among them. Considering the high amount of THC ingested by the patient we consider a possible effect of THC on smooth muscle that could lead to impaired peristaltic activity and to intestinal invagination.

Still immediate newborn behaviors have been observed to these exposed infants consisting in altered arousal patterns, regulation and excitability. Some of these infants manifested increased tremor, exaggerated startle reflexes, poor responses to visual but not auditory stimuli, abnormal high-pitch cries, decreased quiet sleep and increased sleep motility in the first week of life [20]. Although researches have suggested that these behaviors share similarities with neonatal abstinence syndrome due to opioid withdrawal, there are no current data to support a withdrawal syndrome to marijuana exposure.

Conclusions

Therefore, we can conclude that fertility is not influenced by the presence of HL, nor by AVBD chemotherapy. After 6 years since starting AVBD treatment, on a patient known to have HL stage IIB, naturally conceives the first baby and less than a year after that, becomes pregnant again while still nursing.

Also we confirm the positive effects of the cannabis use on symptoms like well-being, appetite and pain in particular. This comes to support the medical use of cannabis. Furthermore, our presentation sustains the antitumor direct effect of oral cannabis take and this makes it a potent and harmless antineoplastic agent.

Conflict of interests

The authors declare no conflict of interests.

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