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Retrospective analysis of a case report of a left ovarian ectopic pregnancy after the former tubal

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Abstract: Up to 2% of pregnancies may be extrauterine. Despite reproductive problems, they might increase the risk of serious complications. We present a case report of a 31-year-old woman with two extrauterine pregnancies — tubal and ovarian, which occurred at the same side with little time difference. In addition, we aimed to examine possible reasons underlying this rare pathology. Thus, surgically removed tissue specimens were morphologically assessed and further compared with specimens from healthy control patients. Telocytes were analysed in detail due to their pivotal role in the female reproductive system. Our study had observational character and obvious limitations typical for a clinical case. Yet, such a clinical case of two ectopic pregnancies has not been previously reported in the literature.

Keywords: ectopic pregnancy, ovary, telocytes, oviduct, ovarian pregnancy.

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Introduction

An ectopic (extrauterine) pregnancy is diagnosed in 1–2% of all pregnancies [1] and occurs in up to 5% with assisted reproductive technologies (ART) [2]. Ectopic pregnancies have been commonly diagnosed in the fallopian tube (an oviduct) [1]. Sometimes women have two pregnancies at one time: intrauterine and ectopic. This con-

dition is called a heterotopic pregnancy [3]. Nontubal pregnancies, i.e. ovarian, in the cervix, myometrium, abdominal cavity, interstitial (intramuscular/proximal) portion of the fallopian tube, or within a cesarean section scar, occur in less than 10% of all ectopic pregnancies [1, 4]. Ovarian pregnancies occur in approximately 0.5–3.2% of ectopic pregnancies. Based on the literature, its incidence ranges from 1 in 7000 to 1 in 40,000 pregnancies [5–8]. The first case of an ovarian pregnancy was described by Dr. Saint Monnissey in the 17th century [9]. However, another scientific source asserts that Mercier (also shown as Mercerus) discovered it in 1614 and described as "a condition separate from a tubal pregnancy" [10]. Boehmer later classified ectopic pregnancy, including ovarian. Cohnstein proposed the first criteria for the primary identification of ovarian pregnancy, which Otto Spiegelberg rephrased in 1878 (an intact ipsilateral tube, clearly separate from the ovary; a gestation occupying the normal position of the ovary; a gestational sac connected to the uterus by the utero-ovarian ligament; ovarian tissue in the wall of the gestational sac) [9, 11, 12]. The criteria have been used and slightly modified. The fundamental parameter was the identification of an embryonic sac within the ovary, however, Wang *et al.* showed that it is not an obvious criterion [12]. Ectopic pregnancies occur in humans but are rarely diagnosed in animals [13].

The oviduct is part of the female reproductive tract and consists of four parts: the infundibulum, the ampulla, the isthmus, and the intramural or interstitial portion [14, 15]. Histologically, it has several tissue types: serosa, smooth muscle, subserosa, lamina propria, and mucosa layers [14]. Based on literature data, the oviduct is essential for fertilization, except for in vitro fertilization, due to specific microenvironment and paracrine signaling [12, 13]. The cellular diversity of oviducts stresses their importance for fertility. Previously, we morphologically assessed human oviducts in search for possible reasons for infertility, underlining the pathophysiological role of impaired muscular contractility and ciliary motility in the tubal factor infertility genesis [16]. An interaction between an embryo and the tubal microenvironment based on paracrine signalling predetermines the possibility of an appropriate transport into the uterine cavity and implantation [17].

Herein, we report a unique clinical case with the history of two ectopic pregnancies on one side, an ovarian after the tubal one, with the former surgically removed. In this case report, we also aimed to examine possible reasons underlying this rare pathology. Thus, surgically removed tissue specimens were morphologically assessed and further compared with specimens from healthy control patients. Telocytes (TCs) are explained in detail due to their pivotal role in the female reproductive system in muscular contractility, tissue repairing, intracellular signaling, angiogenesis, and fibrosis development [18–20].

Material and Methods

Subjects

Oviductal (after left tubectomy) and ovarian (after left ovariectomy) tissue samples were obtained from a 31-year-old woman for the morphological assessment. The control group comprised eight patients (39.2 ± 4.1 years) after a laparoscopic hysterectomy without any signs of uterine myoma or inflammatory processes in the oviducts. Hysterectomy was performed according to the standard protocol. Oviductal (right and left) tissue samples from all eight patients were assessed morphologically. Postsurgical histological examination of the uterus and fallopian tubes revealed no signs of malignant tumors.

Ethical Approval

The study was performed according to the ethical, regulatory, and scientific principles governing clinical research. All surgical samples were retrieved with the approval of the Jagiellonian University Bioethical Committee (Protocol No. 1072.6120.48.2018) using procedures that conformed to the guidelines of the Declaration of Helsinki.

Tissue Processing

Fresh tissue specimens from hysterectomy were collected, quickly rinsed thoroughly with PBS (phosphate-buffered saline, 0.01 M, pH = 7.4). Fixation was performed in 4% phosphate-buffered paraformaldehyde with embedding in paraffin. Sections were cut and mounted on poly-L-lysine-coated glass slides. While, all tissue samples from the pregnant patient were obtained as paraffin blocks and after cutting were also mounted on poly-L-lysine-coated glass slides.

Gross histological analysis

For gross microscopic tissue evaluation, sections after deparaffinization and rehydration were stained with hematoxylin–eosin (H&E staining).

Immunofluorescence staining

Slides were deparaffinated and rehydrated. Incubation with the normal serum (Dako, Glostrup, Denmark) and 0.3% Triton X-100 (Sigma, St. Louis, MO, USA) in PBS was performed at room temperature for half an hour. Then slides were incubated (18 h at 4°C) with the following primary antibodies: polyclonal rabbit anti-c-kit (A4502, Dako,

Glostrup, Denmark; 1:100); polyclonal goat anti-PDFFR alpha (AF-307-NA,R&D Systems, Minneapolis, Minnesota, USA; 1:100); monoclonal mouse anti-vimentin (Clone V9, Dako, Glostrup, Denmark; 1:50); monoclonal mouse anti-CD34 (M7165, Dako, Glostrup, Denmark; 1:100); monoclonal rabbit anti-CD34 (ab81289, Abcam, Cambridge, UK; 1:200); polyclonal mouse anti-iNOS (sc-7271, Santa Cruz, Dallas, Texas, USA; 1:100); monoclonal mouse anti-CD31 (C70A, Dako, Glostrup, Denmark: 1:100) and polyclonal rabbit anti-PGP 9.5 (Z5116, Dako, Glostrup, Denmark; 1:100). Incubation with the appropriate secondary antibodies (1h, room temperature) was performed after washing in PBS: Polyclonal Swine Anti-Rabbit FITC (F0205, Dako, Glostrup, Denmark; 1:40); Alexa Fluor 488 Goat Anti-Mouse (115-545-146, Jackson ImmunoResearch, Ely, UK; 1:400); Alexa Fluor 594 Goat Anti-Mouse (115-585-146, Jackson ImmunoResearch, Ely, UK; 1:400); Alexa Fluor 594 Donkey Anti-Goat (705-585-003, Jackson ImmunoResearch, Ely, UK: 1:400); Alexa Fluor 488 Goat Anti-Rabbit (111-545-144, Jackson ImmunoResearch, Ely, UK; 1:400); Alexa Fluor 488 Donkey Anti-Goat (705-545-003, Jackson ImmunoResearch, Ely, UK; 1:400) and Alexa Fluor 488 Rabbit Anti-Mouse (315-545-045, Jackson ImmunoResearch, Ely, UK: 1:400). DAPI nuclear counterstain — UltraCruz® Aqueous Mounting Medium with DAPI (sc-24941, Santa Cruz, Dallas, Texas) or Hoechst 33342 nuclear counterstain (62249, Thermo Scientific, USA) were used in some instances.

Microscopic Analysis

All slides were examined using an MN800FL epifluorescence microscope (OptaTech, Warsaw, Poland) equipped with an Olympus DP74 digital CCD camera (at 200, 400 and 600× magnification). The qualitative analysis was provided in ten consecutive high-power fields of vision (400×) using Multiscan 18.03 (CSS, Warsaw, Poland), a computer-based image analysis system. To avoid bias, two independent specialists assessed all the samples (each blind to the other) without any special knowledge of any clinical parameters or prognostic factors.

Neuronal cell bodies and fibers of the autonomic nervous system were evaluated based on their localization, morphology and immunopositivity (PGP 9.5- and iNOS-immunopositive fibers and cells) [21]. Telocytes (TCs) were detected due to the double immunoreactivity for the former described markers (CD34/ PDGFRα and c-kit/vimentin immunopositive cells) and their typical localization. DAPI and Hoechst staining were used to demonstrate the cellular structure of TCs and to ease the morphological assessment.

Biochemical blood tests

5 ml of blood samples from the medium cubital vein were collected in plastic tubes and incubated for 30 min at 4°C to induce clot formation. Centrifugation at 1500× g for 20 min at 4°C (Megafuge 1.0R, Heraeus Instruments, Germany) was performed, and serum samples were kept frozen in small volumes at –20°C until further analysis. All measurements were performed in duplicate. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, and anti-Müllerian hormone (AMH) levels were determined using photometric assays measured with Roche/Hitachi Cobas 6000/e601, Roche/Hitachi Cobas PRO/e801, and Cobas 8000 analyzers.

Results

Case report

A 31-year-old, third-pregnant woman visited the Emergency Room with severe pain in her lower abdomen. The patient reported amenorrhea around 11 weeks and had a positive pregnancy test. She had a history of one vaginal delivery with the manual removal of the placenta (retained placenta) and surgical removal of the left oviduct six months earlier (the ectopic pregnancy was in the isthmic part of the left oviduct, near the uterine horn). During the physical examination, the patient had an acute abdomen with positive Blumberg symptoms (BP 110/80 mmHg, HR 90/min, body temperature — 36.7°C). Transvaginal ultrasound examination revealed that the uterus body size was 4*5 cm with homogeneous myometrium, and the linear endometrium was 3 mm. The right ovary had a typical size and structure; the left ovary contained a heterogenous structure around 4.7 cm in diameter, and the pouch of Douglas contained about 3 cm of free liquid (Fig. 1).

Blood test results were the following: hemoglobin 11.7 g/dl (normal range 13–18 g/dl), hematocrit 34.6% (normal range 37–47%), platelets 207.000 per microliter (normal range 150.000–400.000), and β chorionic gonadotropin 5239 mIU/ml (non-pregnant women are below 5 mIU/ml).

Due to the intensification of pain symptoms, a transvaginal ultrasound examination was repeated, showing an accumulation of free fluid in the pouch of Douglas, a decrease in hemoglobin (9.7 g/dl) and hematocrit (28.7%) levels, and platelets count (158.000 per microliter). After analyzing the patient's physical status and blood test results, it was hypothesized that she had a ruptured ectopic (ovarian) pregnancy. Urgent laparotomic surgery was performed. After opening the abdominal cavity, a bleeding tumor on the left ovary was observed (adhesion between the uterine horn and the mass was revealed). The tumor was resected together with the ovary (Fig. 2).

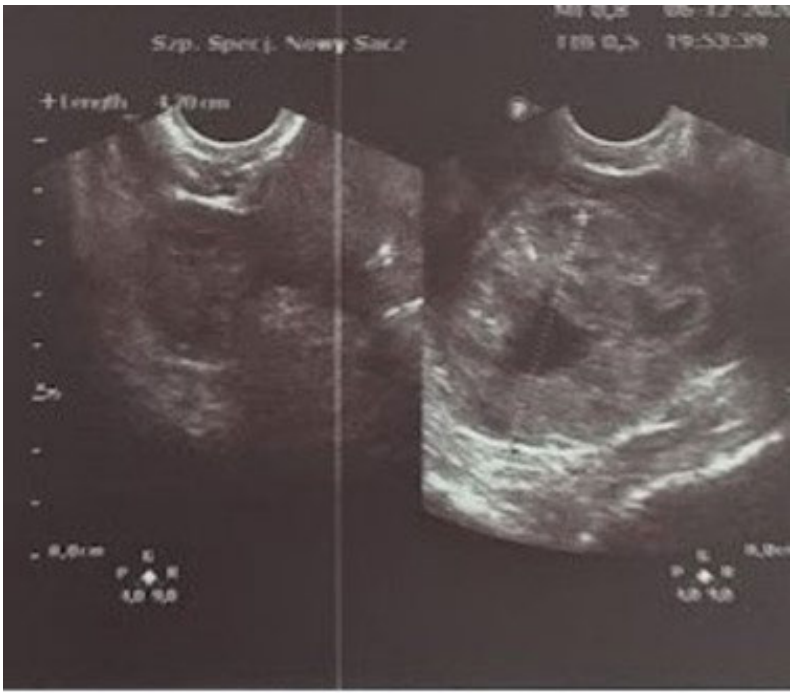

Fig. 1. Transvaginal ultrasound B-mode scan of the left ovary. The nephrogenic mass with an echogenic outer ring of 4.7 cm in diameter in the left ovary. Pressure applied via the probe could not separate the mass from the ovary.

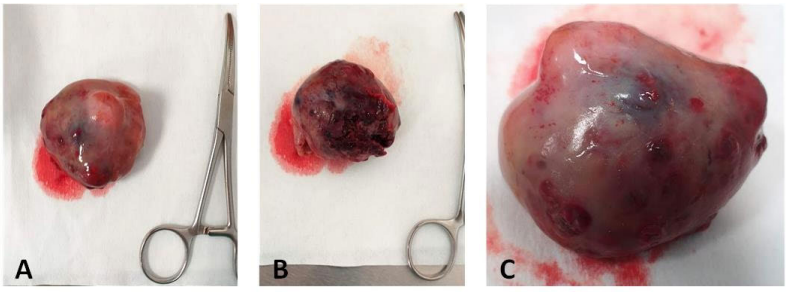

Fig. 2. The removed histological material. The left ovary contained the ectopic pregnancy (tissue samples with signs of bleeding), front (A) and back (B) sides. An enlarged picture of the left ovary with the ectopic pregnancy (C).

The patient experienced no complications post-surgery. On the first day after surgery, the blood level of β chorionic gonadotropin decreased to 3552 mIU/ml, whereas on the third day, it reached 542.9 mIU/ml. The histopathological examination of the received tissue samples verified the left ectopic ovarian pregnancy. The gross

tissue evaluation revealed ovarian tissue samples with a corpus luteum 1.2 cm in diameter on the periphery, and in the centre a red-brown spongy lesion 4 cm in diameter with a visible space of 1.2 cm in diameter — most likely an empty fetal egg.

Histological examination and blood analysis

June 2021 (the left oviduct)

Histological material: Chorionic villi from the 1st trimester and decidual villi in the lumen and the wall of the oviduct. The fetal tissues were not found.

Macroscopic description: The length of the oviduct was 6 cm, and the diameter was between 0.5 and 1.8 cm, filled with blood clots.

December 2021 (the left ovary)

Histological material: The left ectopic ovarian pregnancy. The corpus luteum, corpus albicans, and follicular cysts of the ovary.

Macroscopic description: The ovary was 5.5*5*5 cm in size and 48 g in mass. The external surface was smooth with visible defects of the capsule. On the cross-section: visible residual weaving of the ovary with a corpus luteum of 1.2 cm in diameter on the periphery. A red-brown spongy lesion of 4 cm in diameter was revealed at the center with a visible space of 1.2 cm in diameter and lined by a thin membrane — probably an empty fetal egg.

Biochemical parameters (December 2021): Anti-Müllerian hormone 9.6 pmol/l; follicle stimulating hormone 5.28 mIU/ml; luteinizing hormone 1.41 mIU/ml; progesterone 33.9 nmol/l; estradiol 228.0 pmol/l; sflt 73.70 pg/ml.

Results of the immunohistochemical analysis

Oviductal TCs were identified in the removed Fallopian tube within an ectopic pregnancy. They were located mostly close to blood vessels and within the muscularis layer of the oviduct (Fig. 3). Tissue samples from the ovary had no TCs. Yet, we could not assess either rising or declining tendency of the oviductal TCs within the time frame of our clinical case due to the analysis bias, i.e. a comparison of tissue samples of the oviduct from the only one ectopic pregnancy with nine oviducts from the control group). However, TCs from both groups presented with the same morphology and distribution in the tissue. Our morphological analysis revealed that oviductal tissue samples from the control group had more TCs than those in our clinical case's tissue sample. In our clinical case, some TCs interacted with nerves, illustrating their involvement in the tubes' contractility and peristalsis. NOS-positive nerves were highly expressed in the control group, whereas PGP 9.5-positive nerve fibres were detected in the patient with ectopic pregnancy (Fig. 4–6).

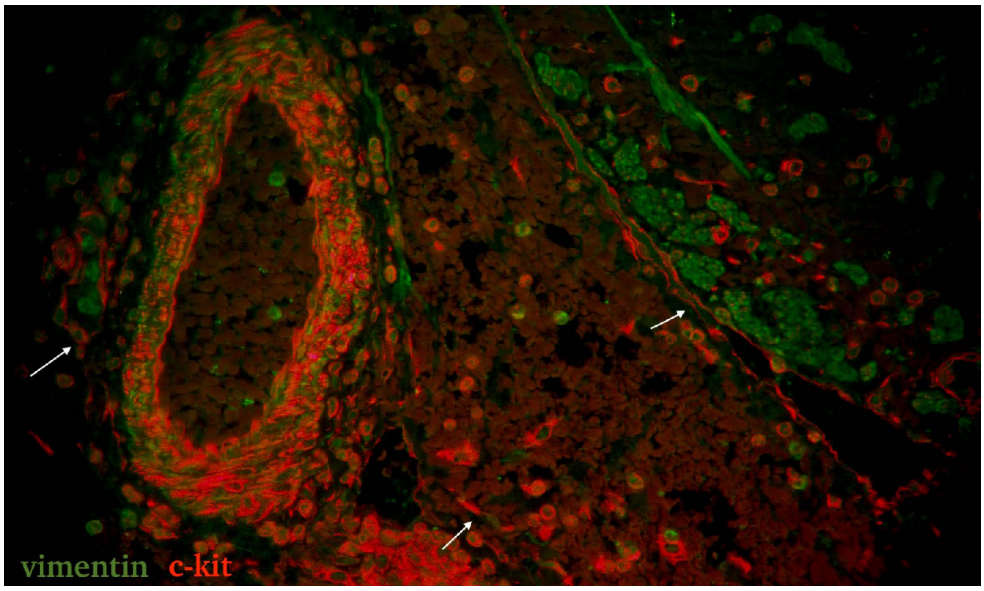

Fig. 3. Double immunolabeling of a human oviduct stained for c-kit (red, Alexa Fluor 594) and vimentin (green, Alexa Fluor 488) of a patient with ectopic pregnancy. Cells with double immunopositivity, with an oval-shaped body and long cellular prolongation were identified as telocytes (marked by arrows). Total magnification: ×400.

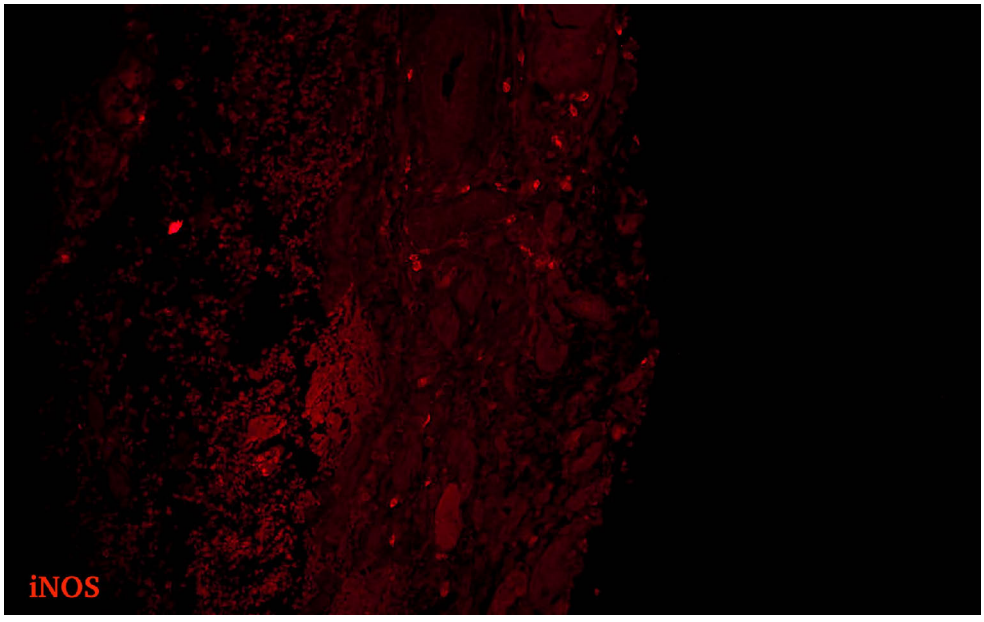

Fig. 4. iNOS-positive neuronal fibers and cells in the oviduct with ectopic pregnancy stained for iNOS (red, Alexa Fluor 594). Total magnification: ×200.

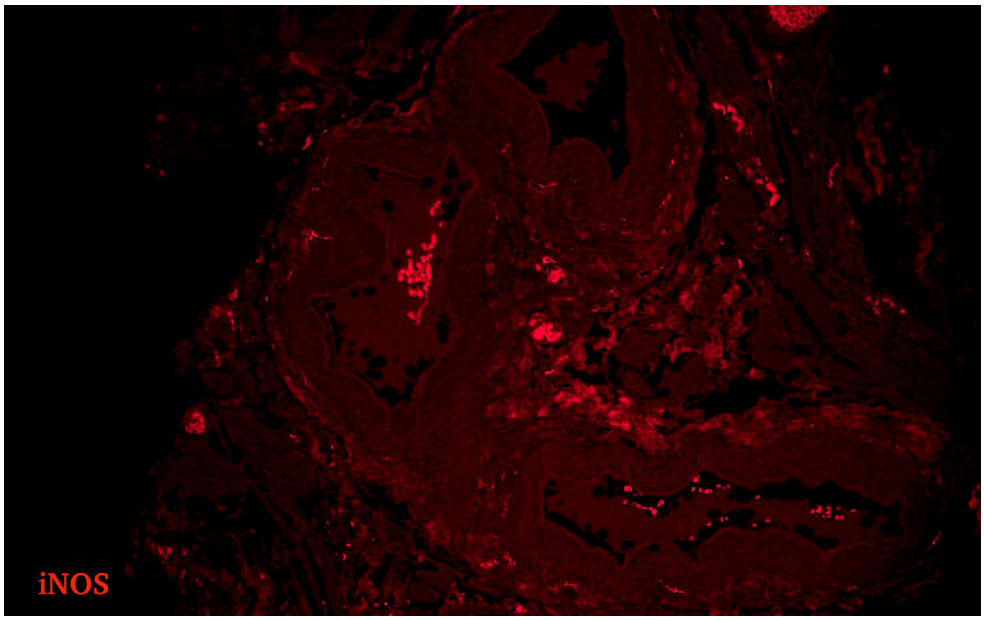

Fig. 5. Oviductal tissue sample stained for iNOS (red, Alexa Fluor 594) from the patient with ectopic pregnancy. More nerve fibers in the tunica muscularis were observed. Total magnification: ×200.

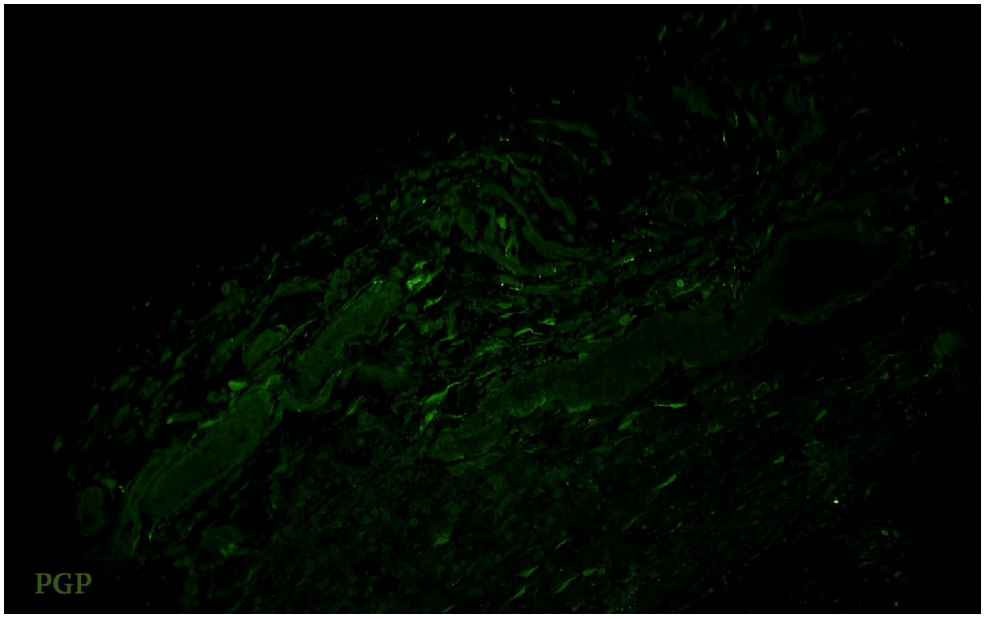

Fig. 6. Oviductal tissue from the patient with ectopic pregnancy stained for PGP 9.5 (green, Alexa Fluor 488). PGP 9.5-positive nerve fibers in the tissue samples were highly present, with the prevalence in the tunica muscularis. Total magnification: ×200.

Discussion

Ectopic pregnancy has risks and should be deeply observed. The retrospective analysis often presents a medical history and possible genesis. Our case has a unicity due to two ectopic pregnancies on the same side in young women. We have not found any previous publications with similar cases. Yet, despite the attractiveness of an ovarian pregnancy from the clinical point of view, we tried to underline problems related to oviducts in the current case. Our patient's two ectopic pregnancies stressed the impossibility of both oviducts — the left oviduct was removed due to the left tubal pregnancy, yet the embryo from the right oviduct was "moved" to the left ovary — transporting embryos into the uterine cavity. Thus, we had two main questions: "Why can it be possible?" and "Why was the second ectopic pregnancy on the opposite of the oviduct side?".

The unclear etiology of an ovarian pregnancy leaves more hypothetical statements that may be proven. Ovarian pregnancies can be explained by the secondary reflux of the fertilized oocyte to the ovary and the implantation on the ovarian tissue [22–24]. Tubal ectopic pregnancies correlate with alterations in oviductal innervation. For instance, Zhang *et al.* observed three cases of tubal ectopic pregnancy without previous infection or inflammatory processes in the oviducts. One patient lost nerves in one or more muscle layers of the oviduct, whereas the other two had abdominal nerve profiles in one or more layers of tunica muscularis of the oviduct [25]. Patients with ectopic pregnancy often have less ciliated epithelial cells. This feature was also common for hydrosalpinx [26]. The extreme state of such a condition—primary ciliary dyskinesia—leads to infertility [27]. The ciliary beat frequency occurs upon stimulating progesterone through ion channels and is accompanied by calcium transport. It stresses the importance of progesterone receptors in the oviducts and all cell types sensitive to progesterone [28]. Tubal TCs are positive for progesterone receptors and may play a role in premature ovarian failure [29, 30]. The rabbit ovarian surface epithelial cells amplify progesterone receptors' alpha expression during pregnancy [29]. These receptors are involved in ovulation mechanisms, postovulatory inflammation genesis, chemotaxis, induced cell proliferation, regeneration, extracellular matrix production, epithelization, and remodeling [31, 32]. Tubal TCs have been mentioned in the context of ectopic pregnancy. Its increased number in patients with tubal pregnancy correlates with decreased motility and disturbances in blastocyst transport to the uterus [33]. We aimed to clarify possible connections between these cells and the risk of the extrauterine pregnancy development. Progesterone receptors' alpha expression is typical for TCs, whereas beta receptor expressions were not detected. In addition, T-type calcium and small-conductance calcium-activated potassium channels were presented in TCs, emphasizing their role in motility and ciliary beat frequency regulation [20]. TCs can also activate the nuclear factor kappa B signaling

pathway and upregulate mRNA levels of pro-inflammatory cytokines such as interleukin-1 and tumor necrosis factor-α [34-36], which are associated with the sloughing of ciliated epithelial cells from the tubal mucosa [17]. Our patient's medical history of two extrauterine pregnancies shows no infections, acute or chronic inflammations, hydrosalpinx, or endometriosis in the oviducts. The cellular and tissue levels are stressed as locations for the cause.

Popescu *et al.* was the first to describe the role of TCs in oviductal peristalsis [37]. They emphasized the electrophysiological properties of TCs and homo- and heterocellular connections with neighboring cells, especially upon contact with smooth muscle cells [16, 18, 22, 37]. Previously, our group explored the role of nitric oxide in oviductal homeostasis, stressing its involvement in signal transduction associated with ciliary beating in the oviduct. Moreover, in animal models, TCs activated peritoneal macrophages and stimulated the production of inducible nitric oxide synthase [16]. Patients with an ectopic pregnancy had higher expression of nitric oxide in tubal samples [38, 39]. Furthermore, TCs were revealed in close vicinity to PGP and NOS-positive nerve fibers. In some cases, we can hypothesize about their indirect interaction. Nitric oxide signaling is indirectly involved in the neurotransmission and pathogenesis of age-related diseases and pathologies in young patients. The interaction between TCs and NOS-positive nerves and their role in stimulating secretion-specific synthase may reflect their indirect involvement in angiogenesis, inflammatory processes, and neuroregulation. Platelet-activating factor (PAF) and platelet-derived growth factor (PDGF) are two proinflammatory mediators important to female fertility. Vascular endothelial growth factor (VEGF) expression occurs upon PAF and PDGF stimulation [40]. The human oviduct contains receptors for PAF (in the subepithelial cells and sometimes in the epithelium) and its enzyme (PAF acetylhydrolase). PAF signaling is crucial for embryo survival and transport into the oviduct due to abnormal smooth muscle contractility and the genesis of ectopic pregnancy [17, 41]. Oviductal fimbriae are positive for platelet-derived growth factor receptor (PDGFR), whose signaling pathway is important for migration and cell differentiation. It is involved in chemotaxis between mature follicle fluids before ovulation and attracts oviductal fimbriae [42]. TCs are strongly positive for PDGFR alpha and VEGF. We are unaware of how they impact oviductal "attractiveness" before ovulation. Different parts of the human oviduct have different expression levels of receptors for growth factors (PDGF and VEGF) [43], while oviductal TCs are positive for both receptor types. Although not appropriate for our current clinical case, inflammation and pro-inflammatory cytokines cannot be underestimated in ectopic pregnancy genesis. Tubal ectopic pregnancy is also associated with increased expression of pro-inflammatory genes (interleukin-6, -8, tumor necrosis factor α) [44]. The epithelial-embryo interactions depend on former inflammatory reactions in the oviductal tissue and cytokine levels [17]. TCs upregulate the mRNA of pro-inflammatory cytokines

(interleukin-1 and tumor necrosis factor-α), are involved in immune homeostasis, and are considered a cellular component of the tumor microenvironment [18, 20, 34].

Based on medical records, our patient had no inflammatory processes in her oviducts or prior gynecological diseases. Only the manual removal of the placenta during the first delivery drew our attention. Retained placenta is a risk factor for bleeding that results from an altered inflammatory response. Are there any common factors between this condition and the patient's two extrauterine pregnancies? Placental growth factor (PGF) is a member of the vascular endothelial growth factors, which are important for ovulation, corpus luteum development (the main source of progesterone production in pregnancy), and placental angiogenesis [45]. PGF may be considered a marker/predictor of preeclampsia and placental insufficiency. We can only speculate that growth factor disturbance was involved in all our patient's gynecological situations (particularly vascular endothelial- and platelet-derived growth factor families). Testing angiogenic markers in our case's tissue samples is impossible due to the heterogeneity of the three clinical pregnancies, lack of fresh material, and difficulty comparing diverse pregnant patient groups. We attempted to answer our two questions addressed at the beginning of the discussion, assuming they are casuistic but not more casuistic than the currently described clinical case. The absence of pathological medical background raises suspicion toward disturbances in intracellular communications, leading to low ciliary beat frequency or bankrupt oviductal contractions. The tubal TCs, due to their properties and contacts, may be involved. The mechanisms are unclear, but numerous glue points between the pathogenic aspects and cellular nature provide opportunities to discuss them in the context of ectopic pregnancy. The second question remains unanswered. However, we believe that some undefined biochemical substances may have stimulated embryo chemotaxis, causing the secondary transport to the left ovary after the primary tubal abortion. We cannot evaluate or prove this explanation, but we can hypothesize its likelihood.

Conclusions

Our clinical case illustrates a rare gynecological condition that occurs in around 2% of pregnancies and the importance of determining new causes. The absence of inflammatory processes and accompanying diseases in our patient proves the significance of oviductal pathophysiological processes and the importance of the oviductal homeostasis for the normal pregnancy development. Local dysmotility and abnormal contractility of human oviducts may lead to the ectopic pregnancy development, including tubal and ovarian as in our clinical case. Importantly, tubal telocytes may be crucial in ectopic pregnancy genesis due to their contact, functions, and their well-recognised role in oviductal physiology.

Author Contributions

Conceptualization, A.W., V.A., M.K.-Ł., J.A.W., and K.G.; methodology, V.A., A.W., A.G., and K.G.; formal analysis, K.G. and V.A.; resources, A.W. and A.G.; data curation, V.A., M.K.-Ł. and K.G.; writing—original draft preparation, A.W. and V.A.; writing—review and editing, A.W., V.A., M.K.-Ł. and K.G.; visualization, A.W., A.G., and V.A.; supervision, K.G. and J.A.W.; project administration, K.G.; funding acquisition, V.A. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

None declared.

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