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Review Article

Fallopian Tube Papilloma: A Systematic Review of Case Reports

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Abstract

Fallopian tube papilloma (FTP) is one of the benign lesions of the oviduct and is a rare proliferative epithelial lesion. Low incidence and underreporting of the disease limit our knowledge of these lesions. These lesions cause a diagnostic dilemma and need to be differentiated from several other conditions of the fallopian tubes both benign and malignant. Fallopian tube papilloma may lead to tubal obstruction and can be a cause of subfertility, ectopic gestation, or mass lesions in the fallopian tubes and hence should be considered as an important differential while managing these women. A high index of suspicion is required, and the final diagnosis can only be made after histopathological results. The reporting of such lesions is important to know the true prevalence of these tumors and to increase our knowledge about these benign neoplasms. This systematic review of case reports was done to enhance knowledge regarding the etiology, natural course, complication, and recurrence of FTP. An electronic search of Scopus, Pubmed, Embase, Web of Science, Google Scholar, and other databases was conducted for case reports and case series published in English from inception till January 2024.

Keywords: Fallopian Tube; Papilloma; Benign disease; Systematic Review.

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Introduction

Fallopian tubes are the seromuscular tubular structures extending from the uterus medially to the ovaries laterally on both sides [1]. Fallopian tubes derived their name after the famous Italian anatomist Gabriele Falloppio who described the anatomy of uterine tubes precisely for the first time [2-4]. Oviducts, salpinges, uterine tubes, or tubes are the other most used terms for fallopian tubes. Fallopian tubes are derived from the cranial portion of Mullerian ducts [5]. Fallopian tubes are around 10-12 cm in length and have a lumen that is approximately 1mm in diameter [6]. Fallopian tubes are composed of three layers, the mucosa, muscularis, and serosa. Tubes have secretory and ciliated cells with predominance of the secretory cells towards the uterus and ciliated cells towards the ovarian end of the tube [7]. In a reproductive-age woman, these cells undergo cyclical changes during the menstrual cycle due to the hormonal variation in different phases of the cycle. Fallopian tubes play an important role in reproduction by helping in sperm transport, sperm capacitation, ovum transport, fertilization, and transport of the embryo to the endometrial cavity for implantation [8]. Normally the tubes are not visualized radiographically unless they are outlined by fluid. However, in the presence of the contrast media or peritoneal fluid the tubes can be seen as paired thin serpentine juxta-uterine structures extending either anteriorly or posteriorly into the cul-de-sac [9]. Hysterosalpingography is one of the excellent methods to visualize fallopian tubes using contrast and is widely used as a diagnostic procedure to rule out tubal blockage while evaluating a woman for subfertility. Diagnostic laparoscopy helps in directly visualizing the fallopian tubes throughout their length and to see their relation to the surrounding structures, as well as to diagnose and treat fallopian tube disease. Tubal function can often be impaired due to inflammation or damage to the tubes by various infections, and benign or malignant lesions of the fallopian tube. These lesions which affect the tubal function often require removal of the tubes via a procedure known as salpingectomy. Salpingectomies are done for ectopic pregnancy, hydrosalpinx, hemato-salpinx, pyo-salpinx, and tubo-ovarian masses. Sometimes the tubes are removed as a routine procedure with hysterectomies for benign or malignant conditions of pelvic organs [10-13]. Primary neoplasms of fallopian tubes both benign and malignant are rare [14-19]. Malignant lesions are slightly more common than benign lesions with a reported incidence of 0.14% - 1.8% of genital malignancies [20]. The true prevalence of benign fallopian tube neoplasm is not known. Malignant neoplasms of the fallopian tubes include serous or endometrioid carcinoma, lymphoma, mixed epithelial-mesenchymal tumors, and metastatic tumors. Among the benign fallopian tube neoplasms are leiomyoma, teratoma, fibroma, adenomatoid tumor, mucosal polyp, lipoma, hemangioma, mesothelioma, cystadenomas, papilloma and metaplastic papillary tumors [21].

Fallopian tube papilloma is one of the rare benign proliferative neoplasms of the oviduct. Fallopian tube papilloma (FTP) is mostly found incidentally while examining the histopathological specimen of the fallopian tube sent after gynecological surgeries are done for some other pathologies like suspected ectopic pregnancy or tubal sterilization specimen or hysterectomy with salpingectomy. There are very few cases of fallopian tube papilloma reported in the literature to date, hence our knowledge about these tumors is limited. This study was done to understand the etiology, natural course, prognosis, and long-term outcome of patients with fallopian tube papilloma.

Material and methods

This is a systematic review of case reports published from 1894 till January 2024. Ethical committee approval was not sought as systematic reviews are exempted from ethical approval. An electronic search of Scopus, Pubmed, Embase, Web of Science, Google Scholar, and other databases was conducted for the case reports and case series published in English from inception till January 2024. The electronic search was done using keywords "fallopian tubes" OR ‘’Oviduct’ OR ‘’Salpinges’’ OR ‘’Uterine Salpinges’’ AND "Fallopian Tube Neoplasms" OR "Fallopian Tube Diseases" AND "Papilloma" AND " Case Reports". Full-length articles, titles, and abstracts identified from the initial search were analyzed by two authors. The reference list of the relevant case reports was also explored. The data was double-checked by the authors for no duplication. The systematic review was planned and reported according to the preferred reporting items for systematic review and meta-analysis guidelines (PRISMA). Review articles and articles in languages other than English were excluded from the review. Two cases from one conference abstract having all the required information were also included in the study*(Figure 1).

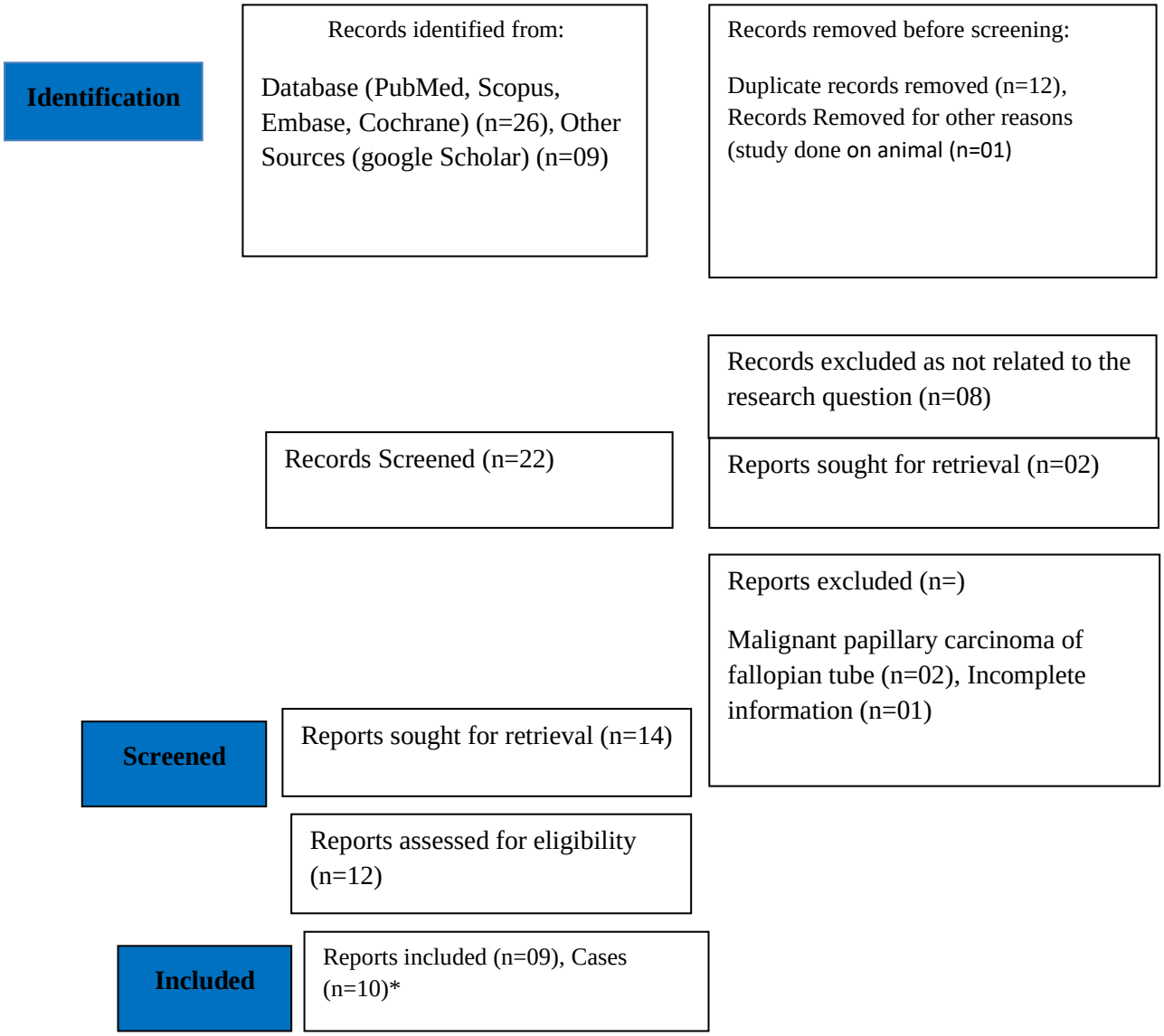

Figure 1. PRISMA flowcharts of the screening process used for the present systematic review
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses

Information regarding the year of publication, age of the patient at presentation, gravidity and parity, clinical symptom at presentation, treatment received, and outcome, follow-up, recurrence, and development of any complication was extracted.

Results

The case reports included were from 1894 till 2024 i.e. over a period of 123 years. Only 10 cases were found to fulfill the inclusion criteria (Table 1) and hence were included in the study.

Table 1. Summary of case reports on fallopian tube papilloma

Case report (Year)	Age	Parity	Clinical presentation	Diagnostic procedure with findings	Treatment	Fallopian tube affected	Site	Follow up	Recurrence	Complications
Kaspersen P[27] (1988)	28	P0	Primary infertility	HSG: Right tubal blockage	Extirpation of medial part of right fallopian tube with tubal re-anastomosis	Right	Ampulla	Uneventful	No	None
Pochiraju M[28] (2014)	27	P0	Primary infertility	DL : 4x 4 cm of bluish swelling in the right fallopian tube	Laparoscopic right salpingectomy	Right	Isthmus	Uneventful	No	None
Mishra S[29] (2023)	37	P1	Secondary infertility	DLH : dilated right fallopian tube and hydrosalpinx	Laparoscopic right salpingectomy	Right	Infundibulum	Uneventful	No	None
Ries E[30] (1894)	34	NM	Pain in the left inguinal region	Ultrasound	Vaginal Pus drainage thrice followed by Laparotomy with BSO	-	Abdominal end	Uneventful	No	None
Rathore R[31]	24	P2	Acute pain abdomen	Ultrasound 4x4 cm	Left salpingectomy with right tubal	Left	Infundibulum	Beta HCG normal	No	None

(2015)			with Vaginal Bleeding per	left tubo-ovarian mass UPT positive Beta HCG 3449.10 mIU/ml	ligation			Uneventful		
Buyucek S et al.[32] (2018)	32	P3	Abdominal pain		Right salpingectomy	Right	Distal end	Uneventful	No	None
	41	P1	Primigravida at 40weeks with oligohydramnios	Intraoperatively para tubal cyst	Cesarean section with para tubal cystectomy with partial salpingectomy	-	Fimbria	Uneventful	No	None
Gisser SD[33] 1986	41	NM	Rapidly enlarging adnexal mass	-	TAH with BSO		Infundibulum	Uneventful	No	None
Narasimhaiah A[34] 2013	45	P5	None	None (surgery done for Procidentia)	VH with Right SO	Right	Fimbria	Uneventful	No	None
Wohlschlaeger J[35] 2018	45	NM	None	Ultrasound finding suggestive of cystic dilation of the distal fallopian tube	Right SO	Right	Infundibulum	Uneventful	No	None

NM: Not mentioned, P: parity, HSG: hysterosalpingogram, DL: Diagnostic laparoscopy, DLH: Diagnostic hysteron-laparoscopy, TAH: Total abdominal hysterectomy, VH: Vaginal hysterectomy, BSO: bilateral salpingo-oophorectomy, SO: Salpingo-oophorectomy

Demographic Profile: The total number of women included in the study was ten. From the literature review, it was seen that most of the women were in the reproductive age group with a median age of 35.5 years (24-45 years). Two nulliparous women who were being worked up for subfertility were included. For three women parity status was not mentioned. The remaining five cases were parous with one or more children.

Presenting symptoms: Out of all the cases, three cases were asymptomatic, and FTP was an incidental finding on histopathological specimen sent after vaginal hysterectomy with bilateral salpingo-oophorectomy in one case, cesarean section with para-tubal cyst removal with partial salpingectomy in the second case and laparoscopic salpingectomy done in the third case for cystic dilatation of fallopian tube found during an ultrasound. Two patients presented with primary infertility, one with secondary infertility, one had pain in the left inguinal area and another patient had abdominal pain. One patient presented with an acute abdomen with a positive urine pregnancy test. One patient had a rapidly progressing adnexal mass.

Site of origin of FTP: Out of all, in six cases the fallopian tube papilloma was found on the right fallopian tube. Only in one case papilloma was found in the left fallopian tube. No specific reason for right-sided predominance was mentioned. FTP was mentioned to be present in the infundibular region in four cases, the fimbria region in two cases, the ampulla in one case, and the isthmus in one case. In one case the distal end of the tube and in another case abdominal end of the tube were mentioned as the site where FTP was found.

Treatment received: Treatment received was specific to the symptom/condition with which the patients presented.

Final Diagnosis: In all the 10 cases FTP was the final diagnosis. The diagnosis was made only after a histopathological examination of the surgically resected specimen.

Complications related to FTP: No short-term or long-term complications related to fallopian tube papilloma have been reported.

Recurrence: No case of recurrence has been reported to date.

Follow-up: Follow-up data was available only for two cases in which the authors reported no complication or recurrence of papilloma. No follow-up data was present for the rest of the cases.

Discussion:

Benign fallopian tube neoplasms are a group of non-metastasizing epithelial tumors of the oviduct. The World Health Organization (WHO) classifies benign fallopian tube neoplasms as papilloma, cystadenoma, adenofibroma, cyst-adenofibroma, metastatic papillary tumor, and endometroid papilloma [22]. Benign fallopian tube neoplasms are often solid and well-delineated. They can be intraluminal or grow on the serosal surface of the tube [23-31]. When intraluminal they can fill the lumen and cause obstruction of the tubal lumen leading to impaired transport of the ovum and hence can lead to subfertility. Due to their intraluminal nature, tubal ectopic pregnancy can also occur. Due to obstruction to the secretions, there can be a collection of the fluid leading to dilated tubes mimicking hydrosalpinx [23-31]. Women with benign fallopian tube neoplasms may remain asymptomatic and can be diagnosed to have tubal masses on ultrasound for any other reason. FTPs that are pedunculated can be misdiagnosed

as adnexal masses. These pedunculated lesions can also present as acute abdominal pain due to torsion of these pedunculated masses.

Fallopian tube papilloma (FTP) is a rare proliferative epithelial benign neoplasm of the oviduct [32-33]. We found only ten cases reported to date which could be either because of low incidence of the condition or underreporting of cases. FTP can be found anywhere on the fallopian tube with infundibulum being the most common site [32]. Fallopian tube papilloma can remain asymptomatic and undiagnosed for a very long time. In some instances, it can present as pain in the abdomen. A history of inflammatory symptoms is usual in cases of fallopian tube papilloma [34-35]. The exact aetiology and pathogenesis of fallopian tube papilloma is not known however local tubal hyperplasia in response to hormonal hyperstimulation or inflammation can be responsible for these proliferative lesions. On gross inspection, benign papilloma of the fallopian tubes appears as a cystic or solid dilated area in the tube [23-31]. Papilloma's are usually found on cut-section of tubes filling the lumen. On microscopy complex branching papillary proliferation of the mucosa is seen which is lined by a single layer of columnar epithelial cells with or without ciliated and secretory cells. No nuclear atypia or mitotic activity is seen, and nuclear cytoplasmic ratio is maintained. The rest of the tube is usually normal-looking and free of any signs of inflammation [23-31]. Proliferative epithelial lesions of fallopian tubes need to be evaluated carefully and should be differentiated from carcinoma in situ. The presence of mitotic activity in such lesions can be an important finding pointing towards pre-invasive carcinoma.

Fallopian tube papilloma usually remains silent. That is why FTPs are mostly found incidentally during fallopian tube surgeries done for any other reason like sterilization operations or salpingectomies for ectopic pregnancies or tubo-ovarian masses. Since these surgeries are mostly done in women of reproductive age, this could be one of the possible reasons for the predominance of fallopian tube papilloma in this age group. Fallopian tube papilloma occurs due to proliferation of the tubal epithelium which can be intraluminal or can occur in the walls of the tubes causing blockage of the tubal lumen. Hysterosalpingography (HSG) or diagnostic laparoscopy (DL) will confirm the diagnosis of tubal blockage in such cases during infertility workup. Kaspersen P et al, reported a case of a 28-year-old nulliparous woman with primary infertility of 5 years duration with a previous history of pelvic inflammatory disease after intrauterine device insertion. She also had a history of a left ovarian cyst and left tubal hydrosalpinx for which the excision of the cyst and tubostomy were done. After an initial infertility assessment which was found to be normal, she underwent diagnostic laparoscopy with chromo-perturbation where the right tube was found to have medial occlusion. The medial part of the affected tube was extirped and the remaining part was re-anastomosed. On gross inspection, the isthmic part of the excised tube was nodular and fibrotic, and microscopic features were suggestive of salpingitis isthmica nodosa. A 0.5 cm papilloma with delicate branching connective tissue, lined by a flat single layer of epithelium, was identified at the center of the tube. The papilloma was obstructing the tubal lumen. Histopathological features confirmed the diagnosis of benign papilloma [23]. Another case of primary subfertility was described by Pochiraju M et al. in a 27-year-old woman whose infertility workup was normal, and she received around nine cycles of ovulation induction with documented ovulation but failed to conceive. She underwent diagnostic hystero-laparoscopy and was found to have a 4x3 cm bluish cystic swelling in the isthmus of the right fallopian tube with intraluminal blockage and the absent portion of the tube in the proximal ampullary region. Finally, right salpingectomy was performed and on histopathology diagnosis of papilloma obstructing the tubal lumen with congenital absence of the tubal portion was confirmed with evidence of complex papillary proliferation in excess to the normal tubal mucosa with

fine stromal fibrovascular core at the obstruction site. The epithelium at the proliferation site had bland nuclei without any mitotic activity [24]. Another case report of secondary infertility was reported by Mishra S et al, where a 37-year-old woman presented with secondary infertility and on diagnostic hystero-laparoscopy a dilated right fallopian tube and hydrosalpinx was found. She underwent a right salpingectomy. The tube was dilated at the distal end and contained watery fluid. On serial cross-section, a 0.8-10 mm papilloma was found obstructing the lumen of the tube. On histopathology a papillary lesion with complex branching and budding pattern, lined by single-layer columnar epithelium with bland basal nuclei with absent mitotic activity was found. This lesion was seen to be arising from the infundibulum of the fallopian tube. On immunohistochemistry, it was positive for wild P52 and had low K67 activity suggesting the diagnosis of benign papilloma of the fallopian tube [25].

Due to proliferation, there can be abnormal mass/dilatation which could be felt as adnexal mass during pelvic examination or found during the pelvic ultrasound. FTP can also be present in patients with pelvic inflammatory diseases (PID) and can be misdiagnosed as tubo-ovarian mass/hydrosalpinx/pyosalpinx. Reis E et al, described the case of a 34-year-old woman who presented with repeated episodes of pelvic inflammatory disease. She also had a history of violent injury to the left inguinal region followed by painful inflammation of the ovaries. Due to the repeated nature of the disease she had to undergo laparotomy and removal of the bilateral appendages. Histopathological examination confirmed the diagnosis of primary fallopian tube papilloma with secondary bilateral ovarian papilloma [26].

Rathore R et al, reported a case of a 24-year-old woman who presented with acute abdominal pain and vaginal bleeding. Her urine pregnancy test was positive with beta hCG 3449.10 mIU/ml. Ultrasound was suggestive of a 4x4 cm tubo-ovarian mass. She was managed as a case of unruptured ectopic pregnancy with left salpingo-oophorectomy with right tubal ligation. On gross examination, the tube was grossly dilated and edematous. On cut-section, a pale-yellow growth of the tubal mucosa at the infundibular region completely obstructing the lumen was seen. On microscopy, complex adenomatous and papillary proliferation of mucosa was identified. The papillae had complex branching patterns and were lined by a single layer of columnar epithelium with bland nuclei and no atypia. Hence the diagnosis of fallopian tube papilloma was made based on histopathology reports. Post-operatively her beta hCG level returned to normal [27]. This case points towards the possibility of the hormone-secreting nature of the tumor but since this is only one case report and no other such case has been reported to date, it is difficult to reach any definitive conclusion. Hence more studies are required to establish the association of raised hCG level with fallopian tube papilloma. A similar case of fallopian tube papilloma misdiagnosed as ectopic pregnancy was presented by Buyucek S et al, the authors described a case of a 32-year-old woman who presented with pain in the abdomen and was operated following a presumptive diagnosis of ectopic pregnancy. She underwent a salpingectomy of the affected tube. On gross examination, the tube had a 3.5x2x1 cm hydropic area. On the cut section, a 0.7x 0.6 cm papillary structure filling the lumen of the tube was identified. A papillary structure with a fibrovascular core lined by tall columnar epithelium was seen on microscopic examination. Based on this finding the lesions were diagnosed as fallopian tube papilloma with no evidence of ectopic gestation [28]. The above two cases suggest that ectopic pregnancy is an important differential diagnosis, and the possibility of fallopian tube papilloma should always be kept in such women who are hemodynamically stable and patients and family should be counseled accordingly.

Gisser SD reported a case of a 41-year-old woman who underwent an abdominal hysterectomy with bilateral salpingo-oophorectomy for a rapidly enlarging adnexal mass. The mass was misdiagnosed as hydrosalpinx. On gross examination, the tube was dilated at the infundibulum due to a pale yellow exophytic lesion. On microscopy, the lesion was seen to be arising from the adjacent contiguous area of fimbrial hyperplasia with features suggestive of papilloma [29]. Narasimhaiah A et al, described a case of a 45-year-old woman who underwent a vaginal hysterectomy with bilateral salpingo-oophorectomy. One of the tubes was around 3cm dilated end near the fimbria with around 1.5 cm grey-white friable tissue within the lumen. On microscopy delicate branching papillae arising from the tissue epithelium were seen. These papillae were lined by a single layer of tall columnar epithelium with the presence of cilia on some of the cells. No atypia or mitotic activity was seen with absent features of inflammation. The features correspond to benign papilloma of the fallopian tube [30]. Another case of such incidentally reported fallopian tube papilloma was described by Buyucek S et al, where a primigravida at 40 weeks period of gestation underwent cesarean section for oligohydramnios and was found to have a para-tubal cyst. She underwent para-tubal cystectomy with partial salpingectomy. Grossly a 2.5 x1.5 cm long gray, white fallopian tube fimbria with 3.5 cm cyst containing serous fluid was seen. The fimbrial end showed excessive papillary structures. Microscopically papilloma was identified beneath the cyst with papillary structures lined by tall bland columnar epithelium suggesting a diagnosis of benign papilloma of the fallopian tube. No recurrence was noted on follow-up. [29]. Wohlschlaeger J et al, reported a case of a 45-year-old lady who underwent surgery for an asymptomatic cystic tumour in the right fallopian tube identified on ultrasound. Intra-operatively a cystic dilated fallopian tube was removed. On incising the dilated tube around 1 cm large brownish friable tumour was found filling the tubal lumen. This lesion was confirmed to be a papilloma of the oviduct in histopathology which showed a broad fibrous papillary structure lined by tufted epithelium with papillary structure with delicate fibrovascular stroma. The epithelium was lined by pseudostratified blunted nuclei of varying size with dense chromatin and inconspicuous nucleoli. The neoplastic epithelium was immuno-reactive for CA-125 and cytokeratin 7. On further analysis the lesion was shown to have a BARF (c.1799T>A) Mutation (V600E) [31].

Evaluation and diagnostic workup: Though benign papilloma of fallopian tubes have a good prognosis and no malignant potential, still a meticulous workup is required to rule out other important benign and malignant conditions. Evaluation will help the treating team to plan appropriate management and surgical approaches to ensure the best outcome for the patient. Patients with fallopian tube papilloma require investigations to rule out other important differentials. Complete blood count with leucocyte count, and erythrocyte sedimentation rate (ESR) to rule out pelvic inflammatory disease (PID). Mantoux test and endometrial biopsy to rule out genital tuberculosis and tubo-ovarian mass. Tumor markers like cancer antigen -125 (CA-125), lactate dehydrogenase (LDH), beta human chorionic gonadotropin (β-hCG), alpha-fetoprotein (AFP), wherever there is doubt regarding associated ovarian malignancy. Ultrasound of the pelvis to know the site, side, and characteristics of the lesion to differentiate fallopian tube lesions from ovarian masses. Ultrasound will also help in differentiating a benign mass from malignant lesions. In case the lesion is large or suspicious Computed tomography (CT) or Magnetic resonance imaging (MRI) studies may be required. In case surgery is planned additional investigations for pre-anesthetic work-up like blood group and cross match, liver function test, kidney function test, serum electrolyte, thyroid function tests (TFT) urine analysis, electrocardiography (ECG), and chest X-ray should be ordered to rule out any high-risk condition requiring attention in the pre- or post-operative period. Since papilloma's are known to have an excellent prognosis and no progression or malignant transformation

has been reported to date, excision through laparoscopy/open surgery is sufficient for treatment. No long-term complications or recurrences have been reported in the literature. More studies on long-term follow-up of these patients are needed. FTPs are commonly seen to develop in a right fallopian tube, though the reason for right-side predominance is not clear. Though the FTP can arise from any portion of the fallopian tube, the distal part of the tube i.e. infundibulum and fimbrial portion are the most common sites of origin. In all the cases the final diagnosis was made after histopathological examination of the tube. In a few cases, even immunohistochemistry for P53 and K67 was done to differentiate the lesion from primary serous carcinoma of the tube. Various neoplastic or non-neoplastic papillary lesions of the fallopian tube can mimic papilloma and need careful differentiation. Salpingitis, hyperplasia due to chronic inflammation, tubercular salpingitis, and metastatic papillary tumor can all mimic papilloma in histopathology. One differentiating feature of FTP from inflammation due to other causes is that in inflammatory conditions usually the whole tube would be involved whereas in papilloma the changes would be localized. Another important benign lesion that needs to be differentiated from FTP is the metaplastic papillary tumor which usually occurs in postpartum women. Metaplastic papillary tumors can be differentiated from papilloma microscopically as they contain broad papillae lined by stratified and tufted epithelium with cells showing abundant eosinophilic cytoplasm and bland nuclei with no atypia [36-38]. Unruptured ectopic pregnancy, hydro/hemato-salpinx, tubo-ovarian mass, salpingitis, reactive hyperplasia of fallopian tubes, benign fallopian tube neoplasm (adenoma, adenofibroma, and papilloma), and fallopian tube malignancy are the most common differentials [39-45].

Since FTP mimics several other benign and malignant lesions of adnexa and needs detailed evaluation and histopathologic confirmation to reach the correct diagnosis. Very few cases of fallopian tube papilloma have been reported in literature to date which could be either due to low prevalence or underreporting of the lesions. Hence reporting of the cases should be encouraged. Further studies are required to see the association of FTP with raised hCG and other tumor markers.

Conclusion: Fallopian tube papilloma is a rare benign lesion of the fallopian tube without any malignant potential and has an excellent prognosis after removal. Since fallopian tube papilloma mimics several conditions both benign and malignant a meticulous workup is required not to miss any malignant condition. Being intraluminal they are one of the important causes of tubal blockage and should always in kept in mind as an important cause of infertility while working up patients. Removal of the FTP is required to relieve the symptoms, reach a final diagnosis and plan further management for optimal outcome of the patient. Confirmation of the diagnosis of FTP by histopathologic examination is a must. Diagnosis of FTP and its reporting is important to know the true prevalence of the lesions and to increase our knowledge and understanding of such lesions. The patient should be followed up to see any recurrence and long-term complications.

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