# AMR Seminar #48 – Short Summary of Cases

**Case 1:** An otherwise healthy 44-year-old woman with complaints of menometrorrhagia underwent hysteroscopic resection of a submucosal uterine leiomyoma.

**Case 2**: This 54-year old woman was found to have an enlarged left cervical lymph node. An excisional biopsy was performed. By report the patient was immunocompetent.

**Case 3**: In 2005 at the age of 13 and 15 years respectively, two sisters with an established diagnosis of Morris syndrome underwent bilateral orchidectomy.

**Case 4:** This previously healthy 6-year-old girl presented with abdominal pain, fever, vomiting, diarrhea and decreased appetite. Intraabdominal lymph nodes were enlarged.

**Case 5:** A 43-year-old woman with von Hippel-Lindau disease underwent a left lower lung lobectomy for resection of a 2.0 x 1.0 cm cystic nodule which had been identified three years prior and had remained stable in size.

**Case 6**: This 37-year-old female was admitted with the main complaint of progressive dyspnea and chest pain. Thorax radiographs disclosed a large well-circumscribed mass in the right lung .

**Case 7:** A 13-year-old girl presented in August 2005 with a history of persistent nasal obstruction for 12 months. On inspection an enlarged nasopharyngeal tonsil was noted posteriorly.

**Case 8**: This is a 57 year-old man with a lung mass incidentally discovered during routine X ray of the chest. No further medical information is available.

**Case 9**: A 38-year-old man presented with a 9 cm liver mass.

**Case 10**: A 79-year-old, gravida 0, para 0, Japanese female presented with lower abdominal distention. A left adnexal mass was found involving her left fallopian tube and omentum.

**Case 11:** A 39-year-old female was referred to our hospital for definitive oncologic surgical excision of a previously diagnosed clear cell carcinoma of the vagina.

**Case 12**: A 63-year-old male patient developed on both forearms ulcerated lesions measuring up to 2 cm in largest diameter that were completely excised.

**Case 13**: Transverse colon mass in a 66-year-old man. The patient became obstructed and a resection was performed.

**Case 14**: A 51-year-old woman with persistent abdominal pain of 5 months that required treatment with morphine derivatives. The CT scan showed an hepatoesplenomegaly with no visible masses.

**Case 15**: This is a 48-year-old man who presented with a left testicular mass. An orchiectomy was performed.

**Case 16:** 50-year-old male smoker with right nasal obstruction and right nasal polyps. No other significant history.

**Case 17:** 67-year-old male presented with right nasal cavity obstruction. CT scan showed a mass in the spheno-ethmoid region extending to the base of the skull.

# AMR SEMINAR #48
# CASE 1

**Contributed by:** David Ben-Dor, MD

**History**: An otherwise healthy 44-year-old woman with complaints of menometrorrhagia underwent hysteroscopic resection of a submucosal uterine leiomyoma.

**Diagnosis:** The specimen which at first glance appeared totally unremarkable consisted of tissue fragments measuring in the aggregate 5x4x1 cm. Histology showed the expected smooth muscle fibers but what was totally unexpected was the very widespread and thorough infiltration by swarms of mostly small slightly irregular lymphocytes, in many places obscuring the smooth muscle which, where visible, appeared undamaged and without atypia. No evidence of vasculitis was found. The infiltrates were limited to the leiomyoma and did not appear to penetrate into adjoining myometrial tissue (to the degree that the latter was included in the specimen). My first impulse was to consider them reactive, possibly secondary to ischemic or mechanical damage, but the lack of a variety of accompanying inflammatory cells along with the mostly monomorphous nature of the infiltrate was troubling and the possibility of a neoplasm had to be entertained.

I then did a Medline search for uterine lymphoma which yielded some intriguing references to articles describing the histology of leiomyomas from women who had received gonadotropin releasing hormone agonists prior to resection. These reports described T cell infiltrates of the same cytologic nature as the ones that I was seeing and implied the pretreatment as the causative factor.

The first logical thing to do was to obtain complementary clinical information. Upon directed questioning I discovered that the patient had indeed prior to surgery received a medication called decapeptyl which is used to reduce the size of leiomyomas making them more amenable to hysteroscopic removal. Following that I had immunohistochemistry performed which showed diffuse staining with CD3, CD43, and UCHL1, with scattered macrophages and clusters of CD20 positive cells. Dr. John Chan was kind enough to perform additional studies which showed the infiltrates to be cytotoxic T cells positive for CD8 and TIA1, with CD56 negative.

Based on the clinical background, the immunohistochemical findings, and the fact that the woman was in otherwise good health at the time (and remains so currently) with no other findings suggestive of lymphoma, the final diagnosis of leiomyoma with (non-lymphomatous) massive T cell infiltrates secondary to treatment with GnRH agonist was made**.**

**Comment:** Multiple articles have been published throughout the previous decade on the histological changes seen in leiomyomas following GnRH agonist treatment (such as Deligdisch et al, 1997). Most of these articles discuss the presence of trophic changes in the tissue which could be the basis for the noted size reduction, such as necrosis, hyalinization, and others, in comparison with leiomyomas taken from patients who did not receive such therapy, with varying conclusions. In two articles (Demopoulos et al, 1997; and McClean and McCluggage, 2003) vascular damage is stressed as a pathogenic mechanism.

Rare articles have been published demonstrating the type of massive lymphoid infiltrate of leiomyomas following GnRH agonist treatment such as seen in this case.

(Bardsley et al, 1998; Crow et al, 1995; Laforga and Aranda, 1999; McClean and McCluggage, 2003; Ohmori et al, 2002). The histological patterns described in most these case reports are similar to each other and to the case being discussed: infiltration of large number of small mature T cells accompanied to varying degrees by B cells, plasma cells, eosinophils, and macrophages (one case discussed by Crow

et al showed a mostly B cell infiltrate with polyclonal plasma cells). The infiltrates are limited to the leiomyoma itself and do not extend beyond it into adjacent myometrial tissue. Ohmori et al also describes tissue and vascular damage in the lesion.

Massive lymphoid infiltrates of leiomyomas can also be seen in the absence of any prior pharmaceutical intervention (Ferry et al, 1989; Botsis et al, 2005). The histological and immunohistochemical features in these circumstances are again similar to those of the cases with a history of GnRH agonist treatment and to the present case: an infiltrate composed predominantly of numerous small T cells with participation to varying degrees by B cells, plasma cells, macrophages, and possibly some eosinophils. In one case report (Chuang et al, 2001) the T cells were positive for TIA-1 as seen in cytotoxic tumor infiltrating lymphocytes. In another report (Saglam et al, 2005), the T cells were CD8 positive and the B cell component was monoclonal, but the latter was not considered sufficient for diagnosis of lymphoma (there was no evidence for clonality of the T cell population based on T cell receptor gene rearrangement studies).

In the above publications, the possibility of lymphoma is included in the differential diagnosis, with the point being raised that primary lymphomas of the female genital tract are usually large B cell lymphomas arising in the cervix. Additionally, some of the papers emphasize the limitation of the infiltrate to the leiomyoma (as seen in the slides distributed) and the continuing good health of the patients (shared by the patient being discussed here) as factors not in favor of lymphoma. Another differential diagnostic possibility is inflammatory pseudotumor, which should show more leukocytes than is seen in the cases that are reviewed.

Other suggested factors implicated in the etiology of this phenomenon where GnRH was not give could include pelvic inflammatory disease, or IUD placement. It is postulated that the medication presumably causes infiltration of cytotoxic T cells and /or vasculitis via an autoimmune reaction.

While use of GnRH agonists is an accepted treatment modality in the management of leiomyoma, in a given case the average pathologist would probably not be aware of their being administered, and as the usual histological effects would be confounded with those of ischemia which are very banal they would probably not draw much attention or be considered unusual. The unusual side effect of such treatment exhibited by this case is admittedly very rare but awareness of its existence by pathologists could help avoid possible overdiagnosis of malignancy in those cases where the treatment can be documented. As this phenomenon can also occur sporadically without any special etiological factor being present, its recognition would be contingent upon recognition of those particular attributes of this condition as described in the cited publications: an infiltration by mostly small cytotoxic T cells limited to the leiomyoma in otherwise healthy women without other evidence of lymphoma.

I would be interested in learning whether other members of the group were confronted by a case such as this. I would also be interested in the opinion of others as to whether molecular studies which were not performed in this case would be indicated to definitively rule out lymphoma. Interestingly, in only one of the above papers were these studies performed (Saglam et al) in a case not involving GnRH treatment. It seems that the other authors were satisfied that the clinical and histological data they had at their disposal was sufficient to conclude that the infiltrates were reactive without having to resort to more sophisticated methodologies.

**References:**

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Laforga JBM, et al. Uterine leiomyomas with T-cell infiltration associated with GnRH agonist goserelin. Histopathology 1999;34:471-472

McClean G and McCluggage WG: Unusual morphologic features of uterine leiomyomas treated with gonadotropin releasing hormone agonists: massive lymphoid infiltration and vasculitis. Int J Surg Pathol 11 (4): 339-344, 2003.

Ohmori T et al: Immunohistochemical study of a case of uterine leiomyoma showing massive lymphoid infiltration and localized vasculitis after LH-RH derivant treatment. Histopathol 41: 273-279, 2002.

Saglam A et al: Uterine leiomyoma with prominent lymphoid infiltrate. Int J Gynecol Cancer 15: 167-170, 2005.

# AMR SEMINAR #48
# CASE 2

**Contributed by:** Gerald Berry, MD

**History:** This 54-year old woman was found to have an enlarged left cervical lymph node. An excisional biopsy was performed. By report the patient was immunocompetent.

**Pathology Findings:** The portion of the cervical lymph node submitted displays the presence of non-caseating granulomas resembling sarcoidosis. The subcapsular sinuses contain scattered yellow-brown, oval, cigar-shaped structures (see accompanying figure). They stain with both GMS and predigested PAS stains.

**Diagnosis:** Hamazaki-Wesenberg bodies in granulomatous lymphadenopathy resembling sarcoidosis.

**Comment:** I thought I would submit this case as an example of a diagnostic pitfall when ordering the perfunctory fungal stains in the evaluation of granulomatous lymph nodes. This peculiar reaction has been well documented in the literature, usually in the form of a case report each decade! These so-called elliptical bodies or yellow-brown bodies most closely mimic sporotrichosis. The important diagnostic clues are their brown pigmentation in H&E stained sections, absence of budding forms and smaller size than *S. schenckii*. They have been most commonly described in the setting of sarcoidosis but have also been reported in portal lymph nodes in primary biliary cirrhosis. The etiology of this degradation product remains unclear. Of note the patient remains well.

**References**

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# AMR SEMINAR #48
# CASE 3

**Contributed by:** Michele Bisceglia, MD

**History:** An established clinical diagnosis of Morris syndrome [1-2] was rendered in two *sisters* at the age of 4 years and 3 months of age, respectively. A karyotype already performed in both sisters was 46,XY. In 2005 at the age of 13 and 15 years respectively, the two sisters underwent bilateral *orchidectomy*. Testes were lodged in inguinal hernial sacs and the surgical intervention in both patients was ended by bilateral inguinal herniorrhaphy. The two patients had female external genitalia, normal for age breast development, absent pubic and axillary hair, no uterus, and a shortened vagina.

**Gross pathological features:** The surgical specimens were represented by a doublet of testes in each cases, which came to our Anatomic Pathology Division at the same time. Testes were sized 4x2x2 cm (right) and 2.8x1.7x2.2 cm (left) in the former, and 2.7x1.2x1.5 (right) and 1.8x1.3x1.3 (left), respectively. On sectioning the cut surface of all testes showed multiple, well-delimited yellowish to tan intraparenchymal nodules as well as an outer polar whitish nodule, rubbery in consistency. The epidydimis was not noted in any of the four testes. The spermatic cord of each testis was seemingly normal on external inspection.

**Microscopical features**: Histologically most of the inner parenchymal nodules were comprised of hamartomatous proliferations of immature tubules surrounded by thick basement membrane and numerous Leydig cells. The seminiferous (nearly non-luminized) tubules were filled with immature Sertoli cells, being completely devoid of germ cells. The outer polar rubbery nodule was represented by a smooth muscle pseudoleiomyomatous body. The epidydimis was not seen in each testis. The vas deferens was not found in each spermatic cord. *Two glass slides enclosed, labelled A (which is relevant to the testis of the latter case) and B (which is relevant to the transverse section of the spermatic cord of the former).*

**Diagnosis:** Familial complete androgen insensitivity syndrome (Morris syndrome or testicular feminization syndrome).

**Comment:** Androgen insensitivity syndrome or testicular feminization (also eponymically known as Morris syndrome) is a form of *male pseudohermaphroditism* (46,XY karyotype), It represents one of the several types of intersex conditions, along with *gonadal dysgenesis* (Turner's syndrome [pts with 45,X0 karyotype], pure gonadal dysgenesis [pts with 46,XX karyotype; pts with 46,XY karyotype or Swyer's syndrome], and mixed gonadal dysgenesis [45,X/46,XY karyotype, or other mosaics]), *Klinefelter's syndrome* (47,XXY; 46,XY/47,XXY; 46,XX), *true hermaphroditism* (46,XX karyotype; other karyotypes), and *female pseudohermaphroditism* (46,XX karyotype with congenital adrenal hyperplasia, maternal ovarian virilizing tumors, maternal ingestion of hormones) [3-4].

Two main types of male pseudohermaphroditism are recognized: the former being represented by a group of diseases, all of which are characterized by a deficient grade of virilization (gonadotropin-Leydig cell abnormalities; testicular regression; testicular steroid enzyme deficiencies [cholesterol desmolase; 3-beta-hydroxysteroid dehydrogenase; 17-beta hydroxysteroid dehydrogenase; 17-alpha hydroxylase]; 5-alpha reductase-deficiency; testicular feminization or androgen insensitivity syndrome), and the latter being represented by persistent mullerian duct syndrome[3-4].

Androgen insensitivity syndrome is an X-linked recessively (or incompletely recessively) transmitted male pseudohermaphroditism (OMIM # 300068). It clinically presents with female external genitalia, a female

body habitus, and breast development at puberty in individuals with a genotypic and gonadic male sex. Vagina is usually shortened; uterus is usually absent or rudimentary; Fallopian tubes are almost always grossly absent; prostate is absent; testes are bilaterally retained either in the abdomen (50-70% of cases) or have descended in inguinal region (20%) or are located both in the abdomen on one side and in the inguinal region on the other side (10-30%). In the inguinal locations testes are often seen in a coexisting hernial sac. Occasionally the testes may be found even in the retroperitoneum [5]. Many affected patients have absent pubic and axillary hair ('hairless pseudofemale'). The hair of the head is described as luxuriant, without temporal balding.

This disease may be sporadic as well as familial. The diagnosis is usually suspected at puberty because of amenorrhea. Not uncommonly the diagnosis is posed at early age because of inguinal hernia or because of a history of an affected sister, and sometimes it may be discovered after marriage or even in advanced age (84 years of age in a seminar case presented by Scully RE) because of an abdominal tumor mass occurrence.

If a slight masculinization of the external genitalia (clitoromegaly/micropenis with partial fusion of labioscrotal folds) and pubic and axillary hair growth is apparent at puberty, the syndrome is qualified as incomplete feminization syndrome, because of partial responsiveness to androgens. Two main phenotypes are known of incomplete feminization syndrome: the former (Reifenstein syndrome: OMIM #312300) is characterized by external male but ambiguous genitalia (severe hypospadia) with male (Wolffian) ducts, which can be easily clinically confused with "pseudovaginal perineoscrotal hypospadia", an autosomal recessive disorder (OMIM # 264600), while the latter displays an apparently normal male habitus except for infertility and gynecomastia ("infertile male syndrome": OMIM # 308370). Although infertile in both variants these patients may have some spermatogenesis.

The patients herein presented were affected by a complete feminization syndrome with a shortened vagina. Androgen insensitivity syndrome is the end result of an end-organ resistance to androgens, caused by an abnormality of the androgen receptors due to abnormal genes (located on long arm of the chromosome Xq11-12) or (more rarely) to a postreceptor abnormality. Familial form (i.e., with more than one affected members in the family, as in the cases herein presented) are not uncommonly encountered. Laboratory endocrinological investigations disclose a normal serum testosterone level and an elevated luteinizing hormone.
Regarding the sexual organ anatomy and development [6-7], these patients exhibit:

- male gonads, and this consistent with the genotype because gonads develop into testes by the gestational age of 6 to 7 weeks under the influence of TDF (testis-determining factor, the product of SRY gene, the sex determining region of located on the distal short arm of the Y chromosome);
- female external genitalia, because the virilization of the urogenital sinus (obliteration of the labioscrotal folds and lower portion of the vagina) is impaired due to the null effect of dihydrotestosterone on end-organs which as above said are quantitatively or qualitatively primarily insensitive (dihydrotestosterone is produced locally in the same end organs from testosterone by the action of 5-alpha-reductase);
- usual absence of the Wolffian derivatives (epididymis, vas deferens and seminal vesicles) because Wolffian ducts are end-organs which do not develop under androgen stimulation due to the receptors abnormalities (occasionally –depending on the variable severity of the disease condition- rudimentary or maldeveloped epididymis may be seen);
- absence of prostate because this is also an end-organ which needs androgen action for its development;
- usual absence of Mullerian derivatives (Fallopian tubes, uterus, and upper vagina) because MIF (Mullerian inhibiting factor) or AMH (anti-Mullerian hormone) is normally produced by Sertoli cells (sometimes rudimentary uterus and Fallopian tubes may be seen likely due to a defect in the secretion of MIF or even to a defect in the action of MIF because of the interfering relative excess of estrogens; a rudimentary uterus may also be found which is often represented by

bilateral smooth muscle bodies medially fused when testes are retained intra-abdominally or by unilateral smooth muscle nodular structures as in the case herein presented);
- breast development (gynecomastia) because of unbalanced estrogen effect.

Testes in androgen insensitivity syndrome are at risk of tumors, which usually occur after puberty, and therefore bilateral orchiectomy is strongly advised immediately before puberty. Testicular tumors seen in this syndrome are hamartomas (as in the two cases herein presented), germ cell tumors (seminomas, and non-seminomatous germ cell tumors), sex-cord tumors (Sertoli cell tumors, and Leydig cell tumor) [5]. Seminoma plus Sertoli cell tumor in the same gonad means androgen insensitivity syndrome (Scully RE, personal communication). Patients with complete androgen insensitivity syndrome are raised and grow up as female. They usually do not need female hormone supplementation. In a survey study secondary sexual development of these women was found satisfactory, as judged by both participants and physicians. Most women were satisfied with their psychosexual development and sexual function. All of the women who participated were satisfied with having been raised as females, and none desired a gender reassignment [8].

The most important differential diagnosis of androgen insensitivity syndrome is versus another form of male pseudohermaphroditism, i.e., 17-beta hydroxysteroid dehydrogenase type 3 (17-ketosteroid reductase) deficiency, an autosomal recessively transmitted disease, the gene of which is on chromosome 9q22, with affected patients also having male gonads and normal 46,XY karyotye [9].

In this latter disease the transformation of androstenedione in testosterone is impaired due to the above enzyme deficiency, and thus external genitalia are more often phenotypically female (ambiguous in 20% of cases). Wolffian derivatives are well developed, and thus the presence of normal epididymis, vas deferens and seminal vesicles is the pathological clue for the correct diagnosis. Prostate which mainly derive from the endoderm of the urogenital sinus and develop under the influence of androgens is absent. The Mullerian derivatives are absent since MIF is normally secreted. Serum testosterone level is obviously reduced. Clinically it must be noted that at puberty (differently from testicular feminization) virilization may occur (pubic or axillary hair growth, man's voice and clitoromegaly) under the effect of elevated level of androstenedione or due to extratesticular conversion of androstenedione to testosterone. Breast development may be observed. The diagnosis should be made before puberty and followed by gonadectomy in cases with complete female genitalia; in the less frequently seen, partially virilized patients, the diagnosis should be made directly after birth, because androgen treatment may result in a nearly normal male phenotype in adulthood, and male sex assignment can be considered. Supplementary hormone administration and psychological care are important medical tools in the management of these latter patients.

**References**


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# AMR SEMINAR #48
# CASE 4

**Contributed by:** John Chan, MD

(Slide number: H 11655-05)

**History:** This previously healthy 6-year-old girl presented with abdominal pain, fever, vomiting, diarrhea and decreased appetite. With a clinical diagnosis of peritonitis, laparotomy was performed. At operation, there was no evidence of appendicitis or peritonitis. Intraabdominal lymph nodes were enlarged, and biopsied. The operative diagnosis was mesenteric adenitis.

**Diagnosis:** Lymph node – Kawasaki disease.

**Comment:** The lymph node shows geographic necrosis with prominent apoptotic bodies. Neutrophils are present in the necrotizing foci (as confirmed by Leder stain), and fibrin thrombi can be identified. Thus a diagnosis of "necrotizing lymphadenitis, rule out Kawasaki disease" was made, even though the scenario appeared to be quite unusual for this disease.

Upon receiving this diagnosis, the clinicians worked up the patient further. The patient had persistent fever after laparotomy. There was a minor degree of DIC, with deranged coagulation profile. Limb edema was present, and serum albumin level was low. The patient soon developed macular rash over the neck and trunk, and then upper limbs and thigh. He also developed bilateral conjunctivitis, red and fissured lips, and strawberry tongue. Echocardiogram showed prominent coronary arteries, with mild dilatation of the left anterior descending branch. With these clinical features, a diagnosis of Kawasaki disease became obvious. The patient was treated with intravenous immunoglobulin and low dose aspirin, resulting in clinical improvement, resolution of the conjunctivitis, and return of the platelet count to normal. Follow-up echocardiogram several weeks later showed normal coronary arteries.

This is a case of Kawasaki disease with unusual presentation. Many years ago, Gerald Berry contributed an excellent example to the AMR Seminar – unfortunately the slide has been destroyed because the tissue fell off with the plastic coverslip. I believe the Club members would enjoy having a "replacement" case of this rare disease in their files.

Message: Kawasaki disease should be seriously considered by any unexplained necrotizing lymphadenitis in patients below the age of 10 years. Additional histologic clues are: (1) presence of neutrophils in necrotizing foci; (2) presence of fibrin thrombi in the small blood vessels outside the necrotizing foci.

# AMR SEMINAR #48
# CASE 5

**Contributed by:** Tom V Colby, MD (TV05-139 With the aid of Julianne Klein, MD)

**History:** A 43-year-old woman with von Hippel-Lindau disease (VHLD) underwent a left lower lung lobectomy for resection of a 2.0 x 1.0 cm cystic nodule which had been identified three years prior and had remained stable in size. Her past medical history was notable for a cerebellar hemangioblastoma and a renal cell carcinoma.

The left lower lobectomy specimen was received fresh and no distinct mass was palpable. Sectioning revealed a 1.0 cm diameter cyst in the hilar region which contained a 0.3 cm papillary excrescence. The Thoracic Surgeon indicated that intra-operatively there appeared to be multiple minute (1 mm or less) cysts throughout the lung but these could not be appreciated in the deflated gross specimen. Microscopically the hilar cyst was lined by a single layer of cuboidal epithelium and contained a blunt branching papillary structure with fibrovascular core lined by similar bland epithelial cells, consistent with a papillary cystadenoma. The surrounding lung showed multiple microscopic cysts lined by similar appearing epithelium, focally forming papillary infoldings, which an exquisitely peribronchovascular distribution. Submission of nearly half of the lobe revealed that this proliferation was widespread throughout the lobe, being identified in 38 of 40 submitted sections (check number). Cytologically the proliferation had areas which were reminiscent of renal cell carcinoma. Immunohistochemical staining of the cyst lining cells revealed diffusely positive staining for cytokeratin 7, TTF-1 (nuclear staining pattern) and vimentin, as well as weak positivity for polyclonal CEA and patchy staining for E-cadherin. CD10, CK20, B72.3 and thyroglobulin were negative.

**Diagnosis:** Unique pulmonary cystic, probably hamartomatous, lesions in the lung in a patient with VHLD.

**Submitted for interest and comments from members of the AMR Club.**

**Comment:** VHLD is an inherited multiple neoplasia syndrome with an incidence of 1 in 36,000 births in the United States. It is an autosomal dominant condition that occurs in about 20% of cases as a spontaneous rather than inherited mutation of the VHL gene. The VHL gene was identified in 1993 (Latif F et al "Identification of the VHL disease tumor suppressor gene" Science 260:1317-20) and is found on chromosome 3p25-26. It functions as a tumor suppressor gene via its gene product VHL protein, a regulator of hypoxia inducible transcription factor 1. Lack of VHL protein activity is associated with increased levels of angiogenic growth factors including vascular endothelial growth factor (VEGF), which result in cell proliferation and neovascularization (Kaelin "Molecular basis of the VHL hereditary cancer syndrome" Nat Rev Cancer 2002; 2: 673) Several hundred types of mutations have been identified in families with VHLD (Beroud et al "Software and database for the analysis of mutation in the VHL gene" Nucleic Acids Res 1998; 26:256-8).

Individuals with VHL syndrome characteristically present in young adulthood with development of typical neoplasms, and often have a corroborating family history. The most common neoplasms occurring in VHLD are renal cell carcinoma, central nervous system hemangioblastomas, retinal angiomas, pheochromocytomas, and pancreatic islet cell tumour. Renal cell carcinomas are of the conventional clear

cell type and are often multiple. Hemangioblastomas occur most frequently in the cerebellum but may also occur in the brainstem and spinal cord.

Other neoplasms reported in association with VHL including: peripheral nerve hemangioblastomas (Giannini C. et al. Mod Pathol 1998; 10: 999), endolymphatic sac tumours (Horiguchi H et al, Mod Pathol 2001;14:727-732), clear cell endocrine pancreatic tumor (Hoang, Mai P. AJSP 2001; 25; 602-609), clear cell carcinoid tumor of the gallbladder (Sinkre, P,A, AJSP2001; 25: 1334-1339), and clear cell papillary cystadenoma of the epididymis and mesosalpinx (Aydin H, AJSP 2005; 4: 520-523).
About 50% of sporadic renal cell carcinoma of the conventional type exhibit loss of HL gene function.

Primary manifestation of VHLD occurs in many organ sites but is distinctly rare in the lung. Apart from a report of multiple hepatic and pulmonary hemangioblastomas (McGrath FP, Clin Radiol 2002; 45:37-9), primary lung neoplasia related to VHLD is unreported.

The current case shows a pulmonary papillary cystadenoma associated with a diffuse peribronchial microscopic epithelial cysts in an individual with VHLD. The incidence of this finding is unknown. It may be an unrecognized manifestation of VHLD in the lung that remains subclinical in affected individuals. The lesion in this case bears a striking histological resemblance to clear cell papillary cystadenoma of the epididymis (Aydin AJSP 29, 4 p520 – similarity to photos in the report), and indeed shares the typical clear cell morphology and vascularity characteristic of VHLD associated neoplasms. The possibility of metastatic renal cell carcinoma was raised in the differential diagnosis, particularty in view of the patient's history of prior renal cell carcinoma. Renal cell carcinoma is a common diagnostic consideration in VHLD since it is so common in this setting, and many of the other neoplasms that may occur are also characterized by clear cell morphology. Although the main cystic and papillary lesion could simulate a metastasis, the diffuse peribronchial proliferation would not be a typical pattern of metastasis.

Parenchymal organ cysts occur in the kidneys and pancreas in VHLD but appear not to have been reported in the lung. The presence of numerous microscopic cysts that could not be readily identified in the deflated lung is morphologically analogous to the finding of multiple microscopic cysts in the kidney in VHLD (Walther MM et al "Prevalence of microscopic lesions in grossly normal renal parenchyma from patients with von Hippel-Lindau disease, sporadic renal cell carcinoma and no renal disease: clinical implications" J.Urol 154:2010-2014, 1995) but does not share an association with lung carcinoma.

# AMR SEMINAR #48
# CASE 6

**Contributed by:** Hugo Dominguez-Malagon

**History**: This 37-year-old female was admitted to the hospital with the main complaint of progressive dyspnea and chest pain. Thorax radiographs disclosed a large well-circumscribed mass in the right lung . The patient was submitted to total pneumonectomy.

*Gross findings*: Al large, well-circumscribed, non-infiltrating mass with pushing borders occupying 90% of the right lung. The cut surface was pale, with a foliaceous appearance resembling a breast fibroadenoma or phyloides tumor.

*Histological findings*: The tumor is composed of club shaped pseudopapillary structures lined by simple cuboidal or columnar epithelium, the stroma is composed of spindle to stellate cells with occasional nuclear atipia, and no mitotic activity.

*Immunohistochemical findings*: The epithelial cells were positive for cytokeratin AE1-AE3, CK7, CK8, CEA and TTF-1. The stroma reacted strongly with vimentin and actin,and focally for desmin. The epithelium and stroma were negative for: CD34, S100, Calretinin, ER and PR

**Diagnosis**: Pulmonary adenofibroma (fibroadenoma of the lung, fibroleiomiomatous hamartoma, adenoleiomyomatous hamartoma).

**Comment**: The overall picture is that of well-circumscribed nodules composed of cores of mesenchymal cells which appear to have incorporated and entrapped adjacent normal epithelial structures. Their resemblance with Mullerian adenofibroma or an epithelial-stromal mixed tumor the breast like intracanalicular fibroadenoma or phyloides tumor is striking, in fact in the initial description by Scarff et al, in 1944, it was called "fibroadenoma of the lung". Only single cases have been reported (two cases by Saul and Cesar in 1993 Histopathology 23:547-551) making a total of about seven cases published to date. All cases followed a benign course, but were small lesions measuring between 0.8 and 2.5 cm in diameter, as the present case a huge tumor, the behaviour should be considered as uncertain.

Regarding the histogenesis, it still is a controversial matter: the possibilities include a variant of pulmonary hamartoma, a mixed neoplasm arising from epithelial and mesenchymal elements, and a fibroma growing in a lobular fashion.

The differential diagnosis includes: pulmonary blastoma, carcinosarcoma, intrapulmonary solitary fibrous tumor and a metastatic sarcoma.

# AMR SEMINAR #48
# CASE 7

**Contributed by**: Göran Elmberger M.D., Ph.D. (K14090-05) Stockholm 051227, Stockholm 051227 Karolinska University Hospital.

**Clinical Summary**: A 13-year-old girl presented in August 2005 with a history of persistent nasal obstruction for 12 months. On inspection an enlarged nasopharyngeal tonsil was noted posteriorly. A hyperplastic adenoid or possibly lymphoma was clinically suspected and biopsy was performed.

**Pathological findings**: Microscopical evaluation shows a 5 mm sized biopsy with an unencapsulated predominantly papillary tumor showing transitional areas from normal and metaplastic nasopharyngeal epithelium to neoplastic epithelium. The papillary fronds are delicate, complex, often arborizing and some of them have hyalinized fibrovascular cores. Parts of the tumor also shows glandular pattern with crowded acinar and alveolar formations. On high power examination the lining epithelial cells are crowded showing cuboidal, columnar and partly pseudostratified organization. Nuclei are small with round to oval shape. There is a slight hyperchromasia but the chromatin pattern is generally bland. Mild pleomorphism and loss of basal polarity are seen. Nucleoli are small, distinct, eosinophilic and often marginal. Cytoplasm is sparse and eosinophilic. Sometimes small supranuclear cytoplasmic secretion vacuoles can be noted. In some areas a hobnail pattern is detected. Cilia and psammoma bodies are not seen. No necrosis. Subtle apoptosis is seen. No mitosis seen in original section.

**Histochemical, IHC and ISH results**: PAS +/- D shows weak positive linear staining of apical membrane but intracytoplasmic vacuolar positivity is not seen. EMA+ (apical membranous), CEA mono+, MNF116+, CK high-, Ck low+, CK5-, CK7+, CK18-/+, CK19-, CK20-, TTF-1++ (see fig), COX-2++, Thyreoglobulin-, Calcitonin-, Calponin-/+, S-100-, Actin HHF35-, GFAP-, Synaptophysin-, Chromogranin A-, AR-, ER-, CDX2-, P21-, P53-, P63-. Proliferation fraction 1-2% (MIB-1). ISH EBER- and HPV- (HR/LR). Diploid.

**Diagnosis**: Nasopharyngeal papillary adenocarcinoma (NPPAC) with TTF-1 positivity.

**Comment:** Initially the sample was worked up according to lymphoma protocol by hematopathologists. Flow cytometry and morphological evaluation did not however confirm any lymphoid neoplasm. The hematopathologist evaluating the sample did note epithelial abnormality and referred the sample to me under the working diagnosis of papilloma or hamartoma.

Further clinical investigation including CT and MR did not show substantial tumor or evidence of bone destruction. Thyroid gland was unremarkable. No evidence of metastases to lymph nodes or other organs. Complete surgical excision via lateral rhinotomy was performed. Only minor tumor remnants were identified in the nasopharynx. Follow-up of 4 months is without evidence of tumor recurrence.

Nasopharyngeal papillary adenocarcinoma is an uncommon low-grade malignant tumor of the nasopharynx. Its clinical and pathological characteristics has been well delineated in a few publications (1-4). This case represents a fairly typical pathology but the patient is one of the youngest reported. The reported age range is 11-64 years. The reason for submitting this case is the bland morphology with risk of underestimating its malignant potential and the newly described (5), rather unexpected TTF-1 positivity.

The reason for performing a TTF-1 stain is the differential diagnostic possibility of metastatic thyroid carcinoma and a vague resemblance to pneumocyte proliferation seen in sclerosing pneumocytoma or papillary adenoma of type II cells in the lung. Absence of staining in thyroglobulin and calcitonin as well as negative clinical and radiological findings regarding thyroid pathology practically rules out the possibility of metastatic disease. TTF-1 stain, originally reported as a specific tissue marker for thyroid and lung (6;7) is one of my absolute favourite markers due to high specificity and sensitivity for lung tumours (8). Later TTF-1 has also been reported in small cell cancer and other neuroendocrine tumors regardless of organ origin. (6;7;9) However, I have also occasionally found it to be positive infrequently and unexpectedly in carcinomas of hypopharynx, tongue base and even in a classical serous adenocarcinoma of the ovary (unpublished observations). The embryological activation of TTF-1 in morphogenesis regarding lung, thyroid and diencephalic structures is well described, and may constitute a base for understanding part of its expression pattern. (10-13) Regarding its positivity in NPPAC I have seen reports published on TTF-1 expression during morphogenesis of Rathke's pouch and from an anatomical point of view one could formulate a hypothesis on NPPAC being a midline tumor related to embryological remnants of Rathke's pouch or possibly some diencephalic remnants in this area.

The significance of the rather strong positivity of cyclo oxygenase 2 (COX-2) is unclear but COX-2 is well known to promote tumor growth and metastasis through stimulation of cell proliferation, invasion, and angiogenesis. (14)

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# AMR SEMINAR #48
# CASE 8

**Contributed by:** Giovanni Falconieri, Italy.

**History**: This is a 57-year-old man with a lung mass incidentally discovered during routine X-ray of the chest. No further medical information is available. The patient underwent lobectomy for a 2 cm mass and the clinical suspicion was cancer. Grossly, the lesion is a grey-white lobulated nodule with apparently sharp circumscription. Microscopically, a moderately cellular lesion with tumor cells enmeshed in a bluish, loose ground substance can be identified. A focal but unequivocal area featuring collection of dense collagen fibers apparently within the inflammatory tissue rich in small round lymphocytes and plasma cells could be recognized (see pictures enclosed). These seem artifactual compaction of ground substance filaments/protein after their likely stromal cell producers regressed, or died. Where vital cells are present, the aggregates appear loose and less fibrillary. Hemosiderin, either free or within macrophages, can be noticed around.

Tumor cells were positive for actins and vimentin and negative for an extended battery of antibodies which included keratins, desmin, S100, CD31, CD34. Congo red was tried and it was negative.

To get to the end of the story, I do not know how to call this. I have enclosed in my differential a myofibroblastic tumor of lung with a prominent inflammatory reaction at the periphery, likely low grade/?inflammatory fibrosarcoma. Any better idea?

Another feature that for me is very unusual is the focal but unequivocal presence of fibrillary aggregates that recall the amianthoid bodies described in myofibroblastic tumors of lymph nodes. Exceptionally (Meister et al, Path Res Pract 187; 1991: 906-911) similar changes have been described in the lung. Regretfully, the half block with such "amianthoid fibers" (provided that the group experts agree about the appropriateness of this term) has almost gone for special stains and is no longer available to obtain an adequate number of recuts to circulate for this seminar. I hope that the enclosed pictures may supplement what is missing on the actual glass slide.

# AMR SEMINAR #48
# CASE 9

**Contributed by:** Andrew L. Folpe, MD

**History:** A 38-year-old man presented with a 9 cm liver mass. His clinical history was notable for a mixed testicular germ cell tumor with embryonal carcinoma, yolk sac tumor and immature teratomatous elements, diagnosed two years previously. At that time was also noted to have a large retroperitoneal mass, and a possible liver metastasis. He received 5 cycles of adjuvant chemotherapy, with bleomycin, etoposide, and cisplatin, with good serochemical response. Following this chemotherapy, his retroperitoneal mass was noted to have shrunk considerably. A retroperitoneal lymph node dissection, segmental left colectomy, splenectomy, and left nephrectomy were performed. The retroperitoneal mass contained residual immature teratoma, with a mixture of epithelial and non-specific mesenchymal elements. The other specimens showed only therapy-related changes. Following this, the liver mass continued to enlarge, and was resected approximately 3 months after the retroperitoneal resection.

**Microscopic description:** Sections from the liver mass showed a large and nearly entirely viable-appearing neoplasm composed of gland-like, trabecular, neural tube-like and nested arrays of uniform, lightly eosinophilic, cuboidal to columar cells, with finely uniform ovoid nuclei, and finely dispersed chromatin. Areas diagnostic of embryonal carcinoma, yolk sac tumor, or obvious mesenchymal or epithelial elements were not identified.

**Immunohistochemical results:** The tumor was strongly positive for CD56 (NCAM), variably positive for synaptophysin and chromogranin A, focally neurofilament-positive, and negative for pan-cytokeratin (AE1/AE3).

**Diagnosis:** Metastatic primitive neuroectodermal tumor (resembling medulloepithelioma), arising in the setting of prior testicular germ cell tumor.

**Discussion:** This is an interesting example of a metastatic lesion from a patient with a testicular germ cell tumor, exhibiting divergent differentiation in the form of what has been referred to in the literature as "primitive neuroectodermal tumor" [1]. It is important to emphasize that these tumors are generally quite different from what we usually refer to as "peripheral PNET", and none have been reported to have EWS gene rearrangements.

The largest series by far of this phenomenon was reported by Helen Michael and co-workers at Indiana University[1]. These authors studied 29 young men with PNET arising in germ cell tumors; 9 with tumors confined to the testes, 8 with both testicular and metastatic lesions, and 12 with metastatic lesions only. PNET arising testicular GCT is quite rare, accounting for less than 3% of all testicular GCT seen at Indiana University. The tumors were further classified as most closely resembling neuroblastoma, medulloepithelioma, ependymoblastoma, medulloblastoma, or peripheral neuroepithelioma (Ewing sarcoma/ peripheral PNET) by a combination of histologic and immunohistochemical criteria. In the testes, 7 cases showed features of neuroblastoma and 10 resembled medulloepithelioma. In metastatic sites, 11 metastases resembled neuroblastoma, 3 resembled medulloepithelioma, 5 resembled peripheral PNET, and one resembled ependymoblastoma. When confined to the testis, the presence of PNET had no impact on patient outcome, with all patients alive at last follow-up. In contrast, the presence of PNET in metastatic sites was a significant adverse prognostic factor, with death from disease in 13 of 19 patients. It was not possible to determine whether the histologic subtype of PNET in metastatic locations impacted on prognosis, although there was a suggestion that patients with neuroblastoma-like metastases did somewhat better. Chemotherapy aimed against GCT did not appear to be effective against PNET arising in GCT.

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# AMR SEMINAR #48
# CASE 10

**Contributed by:** Masaharu Fukunaga, MD (S05-2991#C5)

**History**: A 79-year-old, gravida 0, para 0, Japanese female presented with lower abdominal distention. Computer tomography scan revealed a left adnexal mass measuring 5.0 cm. In laboratory examinations before surgery, serum levels of CA125 and alpha-fetoprotein were 406 U/ml (normal < 35 U/ml) and 242,254 ng/ml (normal < 10 ng/ml), respectively. Intraoperatively, a solid mass measuring 5 cm in the left tube, masses in the pouch of the Douglas, omentum, peritoneum and the subserosa of the colon were found. No abnormalities were observed in the liver. No lymphoadenopathy was noted. A total abdominal hysterectomy, bilateral salpingooophorectomy, omentectomy and tumorectomy were performed. After the operation, chemotherapy including cisplatin was administrated. Serum levels of alpha-protein and CA125 decreased to be within normal range.

The distributed slides were taken from the mass of the omentum.

**Diagnosis**: Hepatoid carcinoma with serous component of the fallopian tube.

**Histology and Comments**: The tumor of the left tube was composed of hepatoid carcinoma (90%) and serous carcinoma (10%) components. The hepatoid carcinoma was histologically characterized by a proliferation of round to polygonal cells arranged in a trabecular, tubular, sinusoidal, papillary or solid pattern. The both components showed an infiltration into the surface of the left ovary, omentum, peritoneum including the pouch of the Douglas and serosa of the colon. Immunohistochemically, the hepatoid carcinoma was positive for alpha-fetoprotein, polyclonal CEA (figure 1), hepatocyte paraffin 1 (figure 2), albumin, epithelial membrane antigen, and cytokeratin (CAM5.2). The positive staining of polyclonal CEA and hepatocyte paraffin 1 indicated hepatocellular differentiation. The former delineated bile canaliculae. Ultrastructurally, the cytoplasm contained abundant ribosomes, moderate amounts of mitochondria and rough endoplasmic reticulum that developed into a meshwork and contained mitochondria within it. Microbile channel-like structures (figure 3, arrow) and desmosomes were occasionally observed.

Hepatoid carcinomas or hepatoid adenocarcinomas arising in stomach, lung, ovary and endometrium were reported. To the best of my knowledge, only one case of hepatoid tubal carcinoma was described (1). Hepatocytic differentiation was also rarely observed in ovarian germ cell tumor and ovarian sex-cord stromal tumors.

The differential diagnosis includes clinically and pathologically hepatoid yolk sac tumor (HYST) and metastatic hepatocellular carcinoma. HYST occurs in the ovary of younger patients and usually in the reproductive age group. Hepatoid carcinoma occurs in generally older patients. The present tumor, which was of tubal origin with a focal serous carcinoma component, was not associated with germ cell neoplastic components or gonadal dysgenesis. Large polygonal cells histologically characterize HYST with abundant eosinophilic cytoplasm growing in compact masses separated by fibrous bands. In most cases, classic yolk sac tumor elements such as reticular pattern or Schillar Duval bodies are found al least focally in HYST. In this particular case the presence of serous carcinoma is a helpful finding in differentiation from metastatic hepatocellular carcinoma. Metastasis is only rarely an initial mode of presentation for hepatocellular carcinoma. The sharp drop in alpha-fetoprotein postoperatively offered convincing support for the diagnosis of a tubal hepatoid carcinoma.

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# AMR SEMINAR #48
# CASE 11

**Contributed by**: Thomas Krausz, MD

**Clinical History:** A 39-year-old female was referred to our hospital for definitive oncologic surgical management of a previously diagnosed clear cell carcinoma of the vagina. Upper vaginectomy, hysterectomy and bilateral salpingo-oophorectomy were performed. There was no residual carcinoma in the surgical specimen , which showed adenosis only (representative slide submitted).

**Additional history:** No evidence of DES exposure. At operation periadnexal adhesions were found. Postoperative course was uneventful apart from focal nodularities in the remaining vagina, which were biopsied on several occasions in the following twelve months. All the biopsies showed focal superficial mucosal ulcerations with underlying deposition of abundant homogenous eosinophilic, amyloid-like material (similar to that seen in the submitted histologic section). On the last vaginal biopsy the possibility of "ligneous vaginitis" was suggested and the histologic review of all the previous specimens revealed the deposition of similar material in the cervix, endometrium, ovaries and periadnexal adhesions. In view of the findings the patient was questioned about possible symptoms of ligneous conjunctivitis in childhood which revealed that indeed she had long-standing conjunctival problems (never precisely diagnosed) and also frequent hoarseness which lasted for many months. Many years ago diagnosis of laryngeal polyps were made (no histology).

**Pathology:** The main finding is the deposition of abundant fibrinous, focally homogenous hyalinized material in association with vaginal adenosis. H&E, histochemistry, immunohistochemistry and EM show that most of the material is fibrin. Stains for amyloid, light chains etc. are negative.

**Diagnosis:** Ligneous vaginitis in association with adenosis.

**Discussion:** Ligneous conjunctivitis is a rare form of chronic conjunctivitis in which patients present with pseudomembranous, "woodlike" lesions of the conjunctiva. In addition to (or occasionally instead of) ocular lesions, many patients have pseudomembranous involvement of multiple mucosal surfaces, including the mouth, nasopharynx, tracheobronchial tree, intestines and the female genital tract. The clinical course of the disease is variable. Patients often present with conjunctival membranes as young children, with some patients progressing to corneal involvement and even blindness, and others showing spontaneous regression. With time, they may develop other symptoms at sites of minor trauma, including gingival hyperplasia and hoarseness. Occasionally, patients may develop life-threatening respiratory distress or even intestinal obstruction secondary to the pseudomembranes. Gynecological involvement often leads to infertility, dysmenorrhea and pelvic pain.

Histologically, this lesion may be easily dismissed by the unwary pathologist. Microscopic examination of the involved mucosal membranes invariably shows subepithelial deposits of amorphous, eosinophilic, hyaline-like material, often with an adjacent acute or chronic inflammatory infiltrate. There may be overlying epithelial ulceration and/or hyperplasia. Histochemical and immunohistochemical stains demonstrate that the amorphous material is predominantly fibrin and fibrinogen admixed with mucopolysaccharide and deposits of plasma proteins such as immunoglobulin and albumin. Stains for amyloid are negative.

In humans, as well as in mouse models, ligneous conjunctivitis has recently been linked to type I plasminogen deficiency, a form of inherited hypoplasminogenemia that is characterized by low levels of active and immunoreactive plasminogen. Type I plasminogen deficiency may be caused by a variety of

homozygous or compound heterozygous mutations of the plasminogen gene. These most likely result in decreased secretion or increased degradation of this critical component of the fibrinolytic system, leading to accumulation of fibrin and impaired wound healing at sites of minor trauma. Significantly, patients with hypoplasminogenemia do not appear to be at increased risk for thromboembolic events, suggesting that there is some redundancy in the fibrinolytic system.

Recently, replacement therapy with intravenous or topical plasminogen has been shown to significantly improve ligneous conjunctivitis and tracheobronchial disease. Some reports have suggested that oral contraceptive pills may also help to boost endogenous plasminogen levels in these patients. Indeed, ligneous inflammation of the mucosal membranes is a serious, but treatable heritable condition which should not be missed by the pathologist.

Subsequent to the suggested diagnosis of ligneous conjunctivitis effecting the gynecologic tract, further investigations showed that the patient indeed has severe hypoplasminogenemia. Study to demonstrate possible mutation of plasminogen gene is currently in progress.

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# AMR SEMINAR #48
# CASE 12

**Contributed by:** Thomas Mentzel, MD

**Clinical Findings:**
A 63-year-old male patient developed on both forearms ulcerated lesions measuring up to 2 cm in largest diameter, that were completely excised.

**Histological Findings:**
The lesion excised with the number I shows features of an ulcerated dermatofibroma with inflammatory cells and focal expression of CD68. The lesion excised under II shows again features of a dermatofibroma, but tumour cells contain more cytoplasm and many cells stain positively for S-100 protein and CD68 respectively. CD1a and langerin were negative.

**Comment:**
Whereas the histology of these two dermal lesions is not very interesting, the clinical findings of the patient are very unusual in our opinion. The patient developed since 1989 an increasing number of small nodular lesions on the whole body with involvement of the trunk, the extremities, and the head and neck region including the eyes (hundreds of lesions are present at the moment). Clinically, the features resemble neurofibromatosis, but histological investigations of multiple lesions revealed features consistent with dermatofibroma, adult xanthogranuloma, and reticulohistiocytoma showing a broad morphological spectrum. All laboratory parameters are normal and there is no hint for a storage disease. Given the unusual features we would favour an unusual form on non-Langerhans cell histiocytosis resembling at least **progressive nodular histiocytoma**.

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# AMR SEMINAR #48
# CASE 13

**Contributed by:** Elizabeth Montgomery, MD

**History:** Transverse colon mass in a 66 year old man. Initially, a small biopsy was received and I was unable to make a diagnosis. In the interim, the patient became obstructed and a resection was performed. This case poses no diagnostic problems on the resection specimen but it is a great example of an inflammatory fibroid polyp with a dramatic and unusual presentation.

**Diagnosis:** Inflammatory fibroid polyp.

**Comment;** The first systematic description of these tumors was provided by J. Vaněk and appeared in the American Journal of Pathology in 1949 (1) although there were prior case reports. Helwig and Ranier coined the present term in the early 1950s(2) but these lesions have been called "gastric submucosal granuloma with eosinophilic infiltration, eosinophilic granuloma, granuloblastoma, neurofibroma, and hemangiopericytoma. The vast majority occur in the stomach where they account for about 3-4% of all gastric polyps(3-9), but they have been reported throughout the gastrointestinal tract(3, 6, 7, 10-16). In Stolte's large comprehensive series, patients with gastric examples were typically 60- 80 years old, but examples are recorded in young adults and the elderly. Most are found in the gastric antrum, but other gastric sites are known. Their endoscopic appearance is that of a smooth submucosal lesion that can be pedunculated or sessile with surface ulceration/erosion in about a third of cases. Presentation is somewhat site specific, in that small intestinal examples can lead to intussusception or obstruction and gastric examples are found in patients with pain and nausea and vomiting. Inflammatory fibroid polyps are probably reactive in nature, but an interesting family with these lesions in females for three generations has been reported ("Devon polyposis"(17, 18)). Flow cytometry in one case showed diploidy(19). A literature search disclosed no reports of cytogenetic anomalies in these polyps. These are benign lesions and seldom recur after excision. Japanese examples have been found in association with gastric dysplasia/carcinoma (presumably based on coincidence)(20)but not Western ones.

Histologically, these tumors are well-marginated but non-encapsulated and affect the mucosa and submucosa. They are composed of uniform spindled cells, mixed inflammatory cells, and prominent vasculature. The spindle cells have amphophilic elongate cytoplasm and pale ovoid to spindle shaped nuclei with variable collagen deposition. Most examples display a whorled "onion-skin" proliferation around vessels and all examples are punctuated by abundant background eosinophils, lymphocytes, and plasma cells. Mitoses are infrequent.

The immunohistochemical and ultrastructural profile of the proliferating cells is that of modified fibroblasts/myofibroblasts, with variable actin but no S100 protein or epithelial markers(10, 12). Some authors believe that their consistent expression of cyclin D1 and fascin suggests that they are of dendritic cell origin(10) but their key feature is consistent CD34 reactivity in small tumors and less consist staining in larger lesions(20). This latter finding, of course, raises the differential diagnostic consideration of gastrointestinal stromal tumors, but the morphology is different and inflammatory fibroid polyps lack CD117. In large examples, sarcomas are often considered but the bland appearance of the proliferating cells and the inflammatory background argue against this interpretation. Note the striking epithelial changes on the eroded surface, which makes one consider an epithelial lesion on mucosal biopsies!

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# AMR SEMINAR #48
# CASE 14

**Contributed by:** Santiago Ramon y Cajal, Spain.

**History**: A 51-year-old woman with persistent abdominal pain of 5 months that required treatment with morphine derivatives. The CT scan showed an hepatoesplenomegaly with no visible masses. Blood analysis demonstrated alteration of the hepatic enzymes. A thrucut biopsy of the liver showed scattered sinusoidal cells with slight atypia not conclusive for malignancy. She began a respiratory insufficiency two weeks before the admittance at our hospital and died. The autopsy was performed.

Necropsy study showed a grayish hepatic nodule 3.5 cm in diameter that microscopically showed a tumor composed of epithelioid cells with mild to moderate atypia and eosinophilic cytoplasm. Tumor cells grew forming vascular channels, following hepatic sinusoids, and with an intravascular growth. The tumor cells were immunohistochemically positive for CD31 and vimentin but were negative for CD34, cytokeratins, EMA, Hep Par-1 and CD68. In addition, immunohistochemistry for HHV8 was negative.

**Diagnosis:** Epithelioid hemangioendothelioma with prominent intravascular dissemination.

**Comment:** Interestingly, our case showed a massive hepatic intravascular dissemination of neoplastic cells, with occlusion of the vessel lumens. The vessels most frequently affected were medium sized veins, but some large veins and, less frequently, some arteries were also affected. There was also intrasinusoidal intrahepatic extension, mostly around the tumoral nodule. Glisson's capsule was also infiltrated. The sinusoidal cells observed in the thrucut biopsy corresponded to hemangioendothelioma cells, but no vessel was affected, so the diagnosis could not be done.

On the other hand, our case showed massive invasion of pulmonary blood vessels, middle-sized veins and some arteries, with extensive alveolar hemorrhage areas. No parenchymal infiltration was observed. The morphologic features were in accordance with the descriptive name that was given in the past to this lesion, as intravascular bronchoalveolar tumor.

Differential diagnosis should be done, in the tumoral area, with cholangiocarcinoma and angiosarcoma, and in the intravascular component with intravascular lymphomas. No factor can predict the behavior of the tumor but those cases with high mitotic counts, angiosarcoma-like areas, or tumor cell necrosis tend to have poor prognosis.

We were impressed with this case, first because we missed the diagnosis in the thrucut needle biopsy (some epithelioid cells into the sinusoids) and because the incredible intravascular dissemination that, we have never seen before.

We are looking forward to hearing your comments.

# AMR SEMINAR #48
# CASE 15

**Contributed by:** Josh Sickel, M.D.

**History**: This is a 48 year old man who presented with a left testicular mass. An orchiectomy was performed.

**Gross findings**: Cut section of the testes revealed a 5 cm light tan, fleshy tumor with focal necrosis. Gross impression was compatible with seminoma. An unusual finding was the presence of an adjacent 2 cm cystic structure filled with colloid material. Delicate loculations are discernible within the cyst. Two gross photographs have been submitted for your review.

**Microscopic findings**: Histologic sections from the solid tumor show classic seminoma with focal necrosis. In addition, variably sized, cystically dilated structures are present, filled with abundant eosinophilic colloid (the resemblance to thyroglobulin is striking!). These cystic structures infiltrate into testicular parenchyma and insinuate themselves between lobules of tumor. Lining cells are cuboidal with minimal nuclear atypia and low mitotic rate. Focal complex microcystic hyperplasia is also noted. Eosinophilic globules are present within lining cells and glandular lumina. Lining cells show the following immunostaining profile: Cam 5.2(+), vimentin(+), TTF(-), thyroglobulin (-). Eosinophilic globules are negative for AFP.

**Diagnosis**: Seminoma with associated hyperplasia and cystic dilatation of rete testis.

**Comment:** The presence of large colloid-filled cysts are unusual in the testis. Although I'd never seen a case, rare examples of struma testis (monodermal teratoma) have been reported in the literature. When I mentioned this possibility of a mixed germ cell tumor to the urologist, he reminded me that an additional diagnosis of teratoma would mean intensive chemotherapy. As noted above, immunostains for thyroid markers were completely negative, ruling out thyroid tissue. I sent slides to Dr. Charles Zaloudek at UCSF pathology in consultation, who rendered the diagnosis of hyperplasia and cystic dilatation of the rete testis. This condition may occur in isolation or associated with various germ cell tumors. The following is an excellent review of this subject: Cysts and epithelial proliferations of the testicular collecting system (including rete testis). Semin Diagn Pathol 2000;17:270-93. Interestingly, hyaline globules have also been reported in similar cases, which may cause confusion with yolk sac tumor (Am J Surg Pathol 1991; 15(1):66-74).

Any comments would be greatly appreciated. I've never seen anything like this!

# AMR SEMINAR #48
# CASE 16

**Contributed by:** Dominic Spagnolo, PathCentre, Nedlands, Western Australia
(Case referred by my colleague Dr. S. Jain, Director, Anatomical Pathology, The Canberra Hospital; outside accession number 05T17033; our accession 05B38544J)

**History*:*** 50-year-old male smoker with right nasal obstruction and right nasal polyps. No other significant history. Followup is short thus far (2 months) but there is no recurrence.

**Pathology:** Two nasal polyps were removed, one submitted as a single 25 x 20x 10 mm polypoid piece of brown tissue, the second as 2 pieces measuring 40 x 40 x 10 mm and 15 x 10 x 10 mm. The histological features were identical in all of these tissue fragments.
There is a florid microglandular/microtubular proliferation in the stroma of this benign polyp, concentrated superficially, and with a suggestion of a "zoning" arrangement around pre-existing epithelial clefts, ducts and glands, but also with areas of more haphazard proliferation. I thought some appeared to bud from native glands/ducts. My colleague Dr. Jain who sent me the case considered this change might be occurring in a respiratory epithelial adenomatoid hamartoma, but I am not convinced of this.

These tubules are lined by a single layer of bland, essentially amitotic, cuboidal epithelium, and they lack a myoepithelial layer. Many of the cells are S-100 positive. This stain also highlighted the fact that some of the small tubules appear to lie within small nerve twigs. The cells are CK7 positive, CK20 negative, and there is no staining with the myoepithelial/basal cell markers p63 and smooth muscle actin.

**Diagnosis and discussion*:*** Open to suggestions please! Opinions ranged from "microglandular adenosis" occurring in a benign polyp, to consideration of a low grade tubular carcinoma. I favor a benign microglandular proliferation, and a broad analogy may be drawn with "microglandular adenosis" in the breast. I have found very little in the literature describing these changes. The changes are similar to those reported in a letter to Histopathology ("Microglandular adenosis arising in chronic paranasal sinusitis" by Chuang S-S and Lin C-N in Histopathology 2000; 36:373-384). Correspondence ensued between our colleague and AMR member, Dr Eusebi (Histopathology 2000; 37:474-481, Eusebi V; Author's reply: Histopathology 2000; 2000; 37:474-481). Dr Eusebi takes issue with the analogy drawn by the authors to microglandular adenosis in the breast, and points out differences from microglandular adenosis in the breast (I take on board his comments).

I am including some images. Unfortunately the S100 stain vanished and it has not been repeated in time.

What do others think of this process? Benign? Malignant? A name? Has anyone seen this before? Looking forward to your comments - thank you.

# AMR SEMINAR #48
# CASE 17

**Contributed by:** Bruce Wenig, MD

**History**: 67-year-old male presented with right nasal cavity obstruction. Clinical evaluation including radiographic imaging revealed the presence of a mass of the spheno-ethmoid region with extension to the base of skull. An intracranial component was not present. Initially, a biopsy was performed followed by a curettage (representative slides provided) as complete surgical extirpation was not possible due to invasion of the skull base.

**Histology**: The light microscopic features include a submucosal diffuse cellular proliferation with focal areas of a vague whorling appearance. The neoplastic cells are relatively uniform with round to oval to spindle-shaped cells nuclei, eosinophilic cytoplasm, inconspicuous to small nucleoli and occasional intranuclear inclusions. Necrosis is not identified and the mitotic rate is low; atypical mitoses are not definitively seen. Prominent vascularity is present, including vessels with associated hyalinization, as well as scattered arborizing ("staghorn" appearing) vessels. Immunohistochemical (IHC) staining included variable reactivity for epithelial membrane antigen, muscle specific actin, CD99, bcl-2, vimentin and neuron specific enolase; no immunoreactivity was present for cytokeratins, CD10, Factor XIIIa, smooth muscle actin, desmin, S100 protein, glial fibrillary acidic protein, caldesmon, CD31, CD34, CD15, HHV8, LCA, CD20, CD79a, CD138, and kappa and lambda light chains. Ki-67 staining showed a proliferative index of approximately 10%. The general consensus was that while the biology of the tumor was uncertain, minimally it should be regarded as a neoplasm of at least low-grade malignant potential.

Many diagnoses were considered. In the initial biopsy (histology similar to what you are seeing in the curetted material), one of my colleagues suggested a possible diagnosis of an atypical meningioma (outside consultation concurred with this possible diagnosis). I was not particularly happy with the diagnosis of an atypical meningioma and although I suggested other possibilities (see below) I did not have a strong feelings relative to an alternative diagnosis. While an atypical meningioma may in fact represent the best (and correct) diagnosis, there are several findings that raise concern about this interpretation. First, the surgeons, including a very experienced base of skull surgeon and an equally experienced neurosurgeon indicated that intraoperative bleeding was quite extensive and in their experience was unusual for a meningothelial tumor. In addition, the histology of this tumor is unusual, in general, and unusual specifically for a meningothelial neoplasm. Meningiomas of the sinonasal tract/skull base overwhelmingly (in my experience) are of the typical histologic type making their diagnosis relatively straightforward. I cannot recall seeing an atypical meningioma of these sites. Certainly, this patient's tumor may represent an atypical meningioma, but that diagnosis may be more one of exclusion resorting to it even in the absence of definite diagnostic features.

On the basis of several findings and literature support, I suggested an alternative consideration, that being a neoplasm within the category of a glomangiomyopericytoma, an evolving tumor category with features that are intermediate between glomus tumor and hemangiopericytoma (HPC). This category may include the sinonasal-type HPC. To this end, the present tumor shows some histologic and IHC features that could allow for classification as a glomangiomyopericytoma/HPC (sinonasal-type). Articles cited to support a possible glomangiomyopericytoma/HPC (sinonasal-type) include: 1) Thompson LDR, et al. Sinonasal-type hemangiopericytoma: a clinicopathologic and immunophenotypic analysis of 104 cases showing perivascular myoid differentiation. Am J Surg Pathol 2003;27:737-49; 2) Rajaram V, et al. Anaplastic meningioma versus meningeal hemangiopericytoma: Immunohistochemical and genetic markers. Human Pathology 2004;35:1413.

I would appreciate help in this case. Do members agree with an atypical meningioma? glomangiomyopericytoma category? something else?