

## **COMMENTS TO AMR SEMINAR #48**

### **CASE NO. 1 – CONTRIBUTED BY DR. BEN-DOR**

**Phil Allen:** Probable uterine leiomyoma with massive lymphoid infiltrates secondary to treatment with GnRH agonist. I cannot recognize it as a leiomyoma on the slide alone and there are some extremely atypical cells with large vesicular nuclei and prominent nucleoli, but I think it matches the descriptions in the literature. I have not previously seen a case. If organ imaging shows no other lesions, I would accept the diagnosis.

**Carlos Bacchi:** This case can really be troublesome diagnostically. Although I thought this was a leiomyoma with inflammation, infiltration by lymphoma crossed my mind but as David rightly said there is no atypia of the lymphoid infiltrate. I have seen this phenomenon of inflammatory infiltrate in leiomyoma but I never thought this could be caused by treatment with GnRH agonist. Thanks David for teaching me that and congratulations for the discussion.

**David Ben-Dor:** In retrospect I was fortunate in that I had the pharmaceutical pretreatment to hang my hat on; if this was one of the sporadic cases without prior treatment the situation would have been that much the more stickier.

**Gerald Berry:** I have not previously seen this degree of lymphoid infiltration in a smooth muscle lesion. It is impressive. The clinical association with GnRH agonist is an important piece of information.

**Michele Bisceglia:** Uterine leiomyoma with non-lymphomatous massive T-cell infiltrates secondary to treatment with GnRH agonist. Thank you, David, for the nice discussion and presentation. This expands the spectrum of tumors with non-lymphomatous massive lymphocytic infiltration, of which likely the most well known is liposarcoma (ref. 1. Kuhnen C, Mentzel T, Sciort R, Lehnhardt M, Homann HH, Debiec-Rychter M. Dedifferentiated liposarcoma with extensive lymphoid component. *Pathol Res Pract.* 2005;201:347-53; and ref. 2. Argani P, Facchetti F, Inghirami G, Rosai J. Lymphocyte-rich well-differentiated liposarcoma: report of nine cases. *Am J Surg Pathol.* 1997;21:884-95). Quite recently we have seen here a case of true gastric "schwannoma" with massive peripheral pseudolymphomatous lymphocytic infiltration: but the infiltrate was mixed (B- and T-cell with some follicles and reactive germinal centers) and was peripherally located.

**Ira Bleiweiss:** Very interesting. There certainly are odd lymphoid aggregates here.

**John Chan:** Thanks to Dr. Ben-Dor I had the opportunity to work up this case. This example is really remarkable. In fact, in some slides, the lymphoid infiltrate is even more massive than shown in the slides being circulated. The cause for the lymphoid infiltrate is not known. Perhaps GnRH causes degeneration of the smooth muscle cells, unmasking some cryptic epitopes, which then evokes a florid host immune reaction.

**Tom Colby:** Agree with diagnosis. I have read about this phenomenon but not seen such a dramatic example.

**Kum Cooper:** Thank you David. We see many GnRH treated leiomyomas with increased cellularity, necrosis, and vascular changes; but I have not encountered this degree of inflammation before. There have also been publications in the recent past of increased lymphocytes and eosinophils in leiomyoma and the rule is to rule out leukemia! Some of the cells especially around blood vessels look rather blastic and primitive.

**Ivan Damjanov:** Very interesting. Never seen it.

**Otto Dietze:** I did not see lymphocytic infiltration of this degree before, thank you.

**Hugo Dominguez-Malagon:** I was not aware of the extraordinary changes that GnRH treatment may cause in uterine leiomyomas, thank you very much for the case and discussion.

**Goran Elmberger:** I have not noted this myself. I would not favor molecular workup. I do find this case interesting and it comes to my mind that it is very recommendable to always look out for signs of generalized lymphohematological disease when one is diagnosing solid tumors. I have a very good teacher and friend in FNA – Professor Sixten Franzen who started out as a hematologist before pioneering the FNA service at Karolinska. He made many diagnoses of anemia or lymphoma while analyzing samples for solid tumors like breast cancer. Most of us do not bother to look for a second disease.

**Vincenzo Eusebi:** Thank you very much for this case and handout. I was not familiar with these changes.

**Giovanni Falconieri:** Though case, David. I agree with you that the lymphoid population is heavy and obscures the myoid quality of the spindle cells. The first impression is of a neoplastic lymphoid infiltrate which was however disproven in this case. I also believe that in a case like this it would be wise to resort to molecular analysis in order to have more insight about the nature of the lymphoid cells. Thanks for the excellent discussion.

**Cyril Fisher:** Extraordinary and interesting case, resembling lymphoma. Thanks for the most informative discussion.

**Christopher Fletcher:** This is a very striking and entirely convincing case of a phenomenon which I have not personally seen previously. In the setting of good clinical documentation (and the prior documentation of such cases in the literature), then there would seem to be little indication for any further molecular testing. It would certainly seem to be a most improbable presentation for any type of T-cell lymphoma.

**Jerónimo Forteza-Vila:** The lymphoid infiltrate atypia attract our attention but the patient development rule out reasonably a lymphoma. The fact that the GnRH analogues can produce an inflammatory infiltrate is very interesting.

**Masaharu Fukunaga:** Thank you very much for the very interesting case and description. My impression was a reactive process. Numbers of mast cells also increase in uterine leiomyoma treated by gonadotropin-releasing hormone agonist.

**Thomas Krausz:** Lymphoma/leukemia was certainly in my differential diagnosis. I accept that treatment-related reactive lymphoid infiltrate is the most likely, however I am a cautious guy, so I probably would have sent it for gene rearrangement study.

**Janez Lamovec:** To me, the lymphoid infiltrate does not seem so monomorphous but rather polymorphous with predominance of small lymphocytes and quite a number of other cells including swollen endothelial cells. Leiomyoma is barely recognizable and the contrast with preexistent myometrium is striking. The overall morphology of the infiltrate and the lack of the latter in adjacent myometrium speak in favor of a reactive lesion. Thank you for this most instructive case.

**Thomas Mentzel:** Thanks for sharing these unusual and biologically interesting findings in a case of uterine leiomyoma.

**Markku Miettinen:** Thank you, this was a new entity to me. Would agree that some effort to rule out lymphoma is prudent

**Elizabeth Montgomery:** I was unaware that these GnRH agonists could create such striking lesional lymphocytosis. Other than the underlying architecture of perpendicularly oriented fascicles, the process appears similar to IMT. I wondered if cases reported as uterine IMT were instead examples of this phenomenon and pulled up a number of them on PubMed - this seemed not to be the case! Thanks for contributing this.

**Santiago Ramon y Cajal:** Very impressive case. Thank you

**Juan Rosai:** This is indeed a good example of the phenomenon of uterine leiomyoma with massive lymphocytic infiltration. I saw the first case of this entity around 1976 in Minnesota. I saw a second case only a few months later and thought of writing them up with a fellow, but I never did. Years later, Scully's paper appeared. As far as I remember, my patients did not have any antecedent conditions, such as therapy with GNRH agonists.

**Elvio Silva:** I have seen several cases of uterine smooth muscle tumors with inflammatory cells with and without previous treatment. In most cases, I thought the lymphoid cells were reactive and I did not study them in detail. Most of the smooth muscle tumors previously treated with GnRH that I have seen had only minimal histologic changes. I wonder if the pathogenesis of this lymphocytic infiltration has a similar explanation to the myomatous erythrocytosis syndrome.

**Dominic Spagnolo:** This is a spectacular and most instructive case. I have not encountered a lymphocytic infiltrate to this degree before in a leiomyoma with or without prior GnRH agonist treatment. I thought the infiltrate atypical prior to reading your excellent discussion. I would have done molecular studies, but that begs the question of what I would then do should a monoclonal rearrangement be shown! In this clinical context, one would have to err on the side of caution.

**James Strauchen:** Wow! This is a fascinating phenomenon I was not previously aware of. Thank you for this informative case.

**Saul Suster:** Thank you David for this fascinating and unusual case. I was not aware of this phenomenon and don't recall having seen a case of uterine leiomyoma like this before. Thank you for the education!

**Lawrence Weiss:** Nice discussion. I have never seen it before. It is definitely not lymphoma.

**Bruce Wenig:** Well, the more I do surgical pathology the more I realize how much I do not know. This is a case in point. Thanks for the education. Without looking at any history or even with it, my initial considerations varied from a possible vasculitic disease process (although vasculitis is not evident), an unusual hematomatous reactive process and a hematomatous neoplasm.

#### **CASE NO. 2 — CONTRIBUTED BY: DR. BERRY**

**Phil Allen:** Hamazaki-Wesenberg bodies in noncaseating granulomatous lymphadenopathy, left cervical lymph node. A most instructive case. As usual, Juan Rosai's textbook is very helpful and includes excellent illustrations on Page 1896 of his latest edition.

**Carlos Bacchi:** Thanks for showing this unique finding in this lymph node with granulomatous lymphadenitis. I had never heard about this (Hamazaki-Wesenberg bodies) before.

**David Ben-Dor:** These corpuscular bodies are quite inconspicuous on H and E (I couldn't find any on an albeit cursory review of the slide) and on PAS- I doubt if I would have picked them up on my own.

**Michele Bisceglia:** Hamazaki-Wesenberg bodies ("yellow-brown bodies"). Honestly have not recognized them, until I looked at the attached images. Paul Wakely presented another similar case with associated granulomas as a Quiz case in AMR Seminar #45. Thank you for submitting this case. By the way since you mentioned about the possibility of seeing such yellow bodies even in portal lymph nodes in primary biliary cirrhosis, I would like to add here something which likely is quite notorious, but which I did not know until few days ago. In primary biliary cirrhosis one may come across enlarged abdominal lymph nodes (most often "portal lymphadenopathy") which are sent for histological examination (on frozen in my case) with a suspected diagnosis of lymphoma or metastatic carcinoma. These lymph nodes (with which radiologists and pathologists engaged in liver transplantation are more familiar) are most usually due to prominent expansion of sinuses which are filled with histiocytes engulfing yellow-brown lipofuscin granules (Ref. 1. Hubscher SG, Harrison RF. Portal lymphadenopathy associated with lipofuscin in chronic cholestatic liver disease. J Clin Pathol 1989;42:1160-5; and ref. 2. Outwater E, Kaplan MM, Bankoff MS. Lymphadenopathy in primary biliary cirrhosis: CT observations. Radiology 1989;171:731-3). These yellow brown granules in sinusoidal histiocytes in primary biliary cirrhosis (and which can be seen even in other different chronic cholestatic epatopathies) are Ziehl-Neelsen positive and argentaffin (Bielschowski positive). Likely the yellow brown pigmented granules present in portal (abdominal) lymphadenopathy in cholestatic liver epatopathies –as in my recent case- are Hamazaki-Wesenberg bodies (I called them "lipofuscin granules"). Thus, Hamazaki-Wesenberg bodies make part of a group of detritus and indigestible residues which can be confused with fungal yeast and spores (see also Seminar #19, case 3, by John Chan regarding mysospherulosis, another pseudomycotic condition).

**Ira Bleiweiss:** These look like foreign body granulomas to me. I would not have considered sarcoid here.

**Tom Colby:** Agree that Hamazaki-Weisenberg bodies are present. They appear to be primarily in sinus histiocytes (as they usually are) and I was more intrigued with what was actually causing the lymphadenopathy which appears to be a combination of scattered granulomas, small nodular foci of hyaline fibrosis, and some reactive changes with immunoblasts. Sarcoid could make the granulomas (and a few Schaumann bodies are present) and the sclerosis so I suppose that is most likely. I suspect HamazakiWeisenberg bodies are most frequently described in sarcoidosis because that is the situation in which we see lymph node biopsies and frequently search on special stains for microorganisms. I see them not infrequently in hilar and mediastinal lymph nodes (but I suppose those are the nodes that I see a lot of). I am not aware of any study that has actually tried to identify the frequency of Hamazaki Weisenberg bodies.

**Kum Cooper:** A subtle example (at least on my slide). We had a case about three years ago that had far more bodies but without granulomas.

**Ivan Damjanov:** Agree

**Otto Dietze:** Thank you for this contribution, I was not aware of this before.

**Hugo Dominguez-Malagon:** Never heard of Hamazaki-Wesenberg bodies, thank you for the case

**Goran Elmberger:** That's beautiful. Will keep my eyes open.

**Vincenzo Eusebi:** No H-W bodies in my section.

**Giovanni Falconieri:** Wow, amazing indeed. Obviously I don't know the entity at issue. Thanks for this educational case.

**Cyril Fisher:** Very nice case, thanks for the helpful illustrations

**Christopher Fletcher:** I have to be honest and say that I don't think that I would have spotted these bodies if I were signing this case out as a regular surgical – thanks for educating me!

**Jeronimo Forteza-Vila:** It's important to know about Hamazaki-Wesenberg bodies, because it can be confused with fungi. Thanks for this case.

**Masaharu Fukunaga:** Dr. Berry, thank you very much. This is my first time to see Hamazaki-Wesenberg bodies in granulomatous lymphadenopathy.

**Thomas Krausz:** Instructive case, thank you. In view of the granulomas, I think, the patient needs follow up.

**Janez Lamovec:** I thought these were some type of fungal granuloma and didn't know of those bodies. Thank you for the lesson.

**Thomas Mentzel:** To be honest I would miss these bodies and I`m grateful for the included figure.

**Michal Michal:** In my slide the Hamazaki-Wesenberg bodies were practically absent. I have seen cases where Hamazaki-Wesenberg bodies had been indeed a conspicuous finding seen already at small magnification. I have usually seen in the wasting patients, who lost a lot of weight is a short time span (mostly tumor associated cachexia).

**Markku Miettinen:** Agree on sarcoid like granulomas, could not find the yellow bodies in the section (they were probably also reported in J Pathol 1970; 102:58-60)

**Juan Rosai:** I suppose this could be sarcoidosis, but it could also be any other kind of burnt out granulomatous inflammation. Actually, the low power appearance is not particularly suggestive of the distribution or shape of sarcoid granulomas. The case is of interest because of the presence of the so-called Hamazaki-Wesenberg bodies. They are now known to be non-specific lysosomal type structures, but at one point somebody thought that he had found the etiologic agent of sarcoidosis.

**Dominic Spagnolo:** Further nice example of Hamazaki-Wesenberg bodies (also recent AMR #45/Quiz case 2)

**James Strauchen:** I am glad this is just an artifact, since I missed it entirely!

**Saul Suster:** Nice case. Dr. Wakely also contributed a similar case as a Quiz Case recently.

**Lawrence Weiss:** I didn't fall into that pitfall – I didn't look closely enough to see them.

**Bruce Wenig:** Great case. Glad you sent the images as try as I might, I could not locate the yellow-brown bodies.

### **CASE NO. 3 — CONTRIBUTED BY: DR. BISCEGLIA**

**Phil Allen:** Familial complete androgen insensitivity syndrome (Morris or testicular feminization syndrome). Thanks for the extensive and very learned dissertation Michele.

**Carlos Bacchi:** Interesting case. It is not difficult to see the hamartomatous alterations in both testis but the excellent discussion (as usual by Michele) on Morris syndrome made me learn a lot about this disease.

**David Ben-Dor:** Another very complicated, and equally carefully examined and documented case from Michele, as we come to expect from this very erudite gentleman (this is said in all sincerity). As he is also devoid of pretension and formally doesn't claim to be anything beyond a general pathologist, all I can say is expressed in the Hebrew phrase "kol hakavod" (hats off).

**Gerald Berry:** Beautiful examples of complete androgen insensitivity syndrome. Thank you for the discussion.

**Michele Bisceglia:** My case. Look forward to seeing others' opinions and comments. With Phil Allen's consent and approval I would like to publish this case as a selected case for the AMR Series in Adv Anat Pathol.

**Ira Bleiweiss:** Wow!

**Tom Colby:** Agree with diagnosis.

**Kum Cooper:** Thank you Michele for educating me on this entity. I had heard of testicular feminization syndrome but not of Morris syndrome.

**Ivan Damjanov:** Extensive review, nice. Thanks. I published in the 1970's a Sertoli cell tumor of this type that was removed from an older woman. If I remember correctly she had four husbands, but no children (of course). The tumor was 2.5 kg or so.

**Otto Dietze:** Excellent case and description. I think, many know this only from the literature.

**Hugo Dominguez-Malagon:** Excellent case and discussion, thank you

**Goran Elmberger:** Wow! AR?

**Vincenzo Eusebi:** Thank you for this unusual case.

**Giovanni Falconieri:** Impossible case!

**Cyril Fisher:** Testicular feminization, a great example which is rare to see. Thanks, Michele, for the comprehensive discussion.

**Christopher Fletcher:** The seemingly limitless range of genetic disorders and extraordinary cases from San Giovanni Rotondo continues to be a source of amazement (I suspect to all of us!). Many thanks for sharing this rare pathology.

**Jeronimo Forteza-Vila:** Thanks for this interesting case.

**Masaharu Fukunaga:** Michele, thank you very much for the very unusual case and the description. The lesion seemed to be Sertoli-Leydig cell tumor without history. The histology of the smooth muscle pseudoleiomyomatous body is very interesting.

**Thomas Krausz:** Michele, thank you for the comprehensive discussion.

**Janez Lamovec:** Michele, as usual, thank you for your interesting case and erudite discussion.

**Thomas Mentzel:** Thank you very much Michele for teaching us this rare condition.

**Michal Michal:** Testicular hamartoma associated with androgen insensitivity syndrome. We have seen recently a Leydig cell tumor in association with this hamartoma.

**Markku Miettinen:** Agree on testicular feminization/androgen insensitivity, a testis in a woman w/ male genotype, very nice example on such a testis, also the cord

**Elizabeth Montgomery:** Such an educational treatise. My own knowledge was confined to tales of film stars and fashion models said to harbor this condition.

**Santiago Ramon y Cajal:** Very good update on this rare condition!

**Juan Rosai:** Very typical case of so-called androgen insensitivity syndrome.

**Dominic Spagnolo:** Amazing case Michele, and typically erudite, comprehensive discussion. It's all a little too hard for me to remember all those steroid pathways and what happens when things go wrong!

**James Strauchen:** I have heard of testicular feminization but I have never seen the pathology. Thank you for this fascinating case!

**Saul Suster:** Absolutely fascinating teaching case! Thanks Michele for another fascinoma. I definitely think you should publish this in the AMR series in Adv Anat Pathol.

**Lawrence Weiss:** I hope this discussion is being turned into a paper. The spermatic cord looks like a round ligament.

**Bruce Wenig:** Ditto my comments relative to Case 1 (except for the diagnostic considerations)

#### **CASE NO. 4 — CONTRIBUTED BY: DR. CHAN**

**Phil Allen:** Kawasaki disease, mesenteric lymph node. A wonderful case that I am sure I would have missed if left to my own devices. Thanks for the contribution John.

**Carlos Bacchi:** What a great case! I did diagnose necrotizing lymphadenitis but I didn't think about Kawasaki disease as my first hypothesis. Many thanks John for the case (and the slide for my file).

**David Ben-Dor:** At first glance the geographic necrosis made me think about Kikuchi disease, though the presence of neutrophils and the absence of the characteristic peculiar histiocytic cells would be against that. As in infectious mononucleosis, this case illustrates another situation in which the pathologist is obliged to make a diagnosis of a clinical syndrome based purely on lymph node morphology without the benefit of supportive clinical information (in this case because the syndrome became full blown only after the biopsy was signed out, putting the cart before the horse). Using the latest edition of Prof. Rosai's textbook as a standard, there isn't much in the way of detailed histological description of this entity available for the (mythological?) "bench pathologist", making this situation all the more knotty. It's very helpful to have this slide along with Dr. Chan's as usual clear and detailed description of the histology.

**Gerald Berry:** A second nice example of nodal Kawasaki disease. I now have collected a number of cases of coronary aneurysms secondary to Kawasaki disease.

**Michele Bisceglia:** Lymph node - Kawasaki's disease. In AMR Seminar # 9 (case 1) Gerald Berry contributed the first case of this disease. I joined the club the subsequent seminar, but got from Saul Suster a complimentary copy of the cases description of the previous Seminar. Since then I loved to see another case in order to get a slide to keep for my collection. Apropos of Kawasaki's disease, very recently I could read an interview with Dr. Tomisaku Kawasaki and learned some more about the recognition of the syndrome. I would like to share it here with the rest of the club members: T. Kawasaki was a member of the staff of Pediatrics Dept of the Red Cross Hospital in Tokyo at the time of the discovery of the disease. He observed the 1<sup>st</sup> case in 1961 (he called it "GOK": God only knows). The following year he encountered another case and called it "non scarlatiniform febrile syndrome with desquamation". In 1964, he presented at the Eastern Japan Pediatrician Group Meeting 22 such cases under the name of "ocular mucocutaneous syndrome". In 1967 Kawasaki published 50 cases in the Japanese Journal of Allergy, ending the dispute with the opponents to the theory of this new disease (of unknown etiology) which he identified (the opponent theory was in favour of an atypical variant of Stevens-Johnson syndrome). Regarding the cardiac involvement in "ocular mucocutaneous syndrome" we have to say that initially Dr. Kawasaki believed that the disease was a self-limiting process. It was Dr. Tanata who worked as a chief pathologist in the same hospital and who in 1965 recognized a coronary thrombus at autopsy in a Kawasaki's patient who died and for whom Dr. Kawasaki's diagnosis in life was ocular mucocutaneous syndrome. In 1968 another Japanese paediatrician from St. Lukes Hospital in Tokyo

discovered and presented non fatal cases of ocular mucocutaneous syndrome with electrocardiographic abnormalities (thus cardiac involvement is not always fatal). In 1970 in USA the first cases were recognized by Marita Melish and Rachel Hicks as a syndrome of "fever of unknown origin with spontaneous resolution" in Hawaiian children of Japanese descent: it was in 1973 that the two American doctors recognized their patients as affected by Kawasaki's disease after seeing the photographs of Kawasaki's original patients. Now the disease is recognized worldwide. In 1976 on a proposal by a commission of the Japanese Government the disease was officially named honoring Dr. Kawasaki.

**Ira Bleiweiss:** Necrotizing lymphadenitis.

**Tom Colby:** Beautiful case; thanks John.

**Kum Cooper:** John thank you for this example. My differential included Kikuchi's vs Lupus vs Yersinia. The presence of neutrophils which you demonstrated with the Leder stain will rule out the former and the clinical correlation the latter (although the fibrinous vasculopathy can be seen in lupus as well). The absence of true granulomatous inflammation and necrosis in germinal centres rules out Yersinia. Thank you again! Great pick-up!

**Ivan Damjanov:** Classical. Thanks.

**Otto Dietze:** Convincing case and clinical follow up.

**Hugo Dominguez-Malagon:** Agree with Kawasaki disease, beautiful example.

**Goran Elmberger:** Thanks.

**Vincenzo Eusebi:** Thank you for this instructive case. Without the history I have called the lesion as mesenteric Yersinia lymphadenitis.

**Giovanni Falconieri:** Great case, nicely instructive. Thanks for contributing another collectible item.

**Cyril Fisher:** Great example of Kawasaki disease.

**Christopher Fletcher:** Great case – what a remarkable presentation!

**Jeronimo Forteza-Vila** This case causes problems about the differential diagnosis with Kikuchi-Fujimoto disease, but there aren't the typical histiocytes, neutrophils in the necrosis foci and vasculitis in the necrosis foci typical of that entity.

**Masaharu Fukunaga:** Thank you, John. I have never seen a lymph node with Kawasaki disease. The clinical information and the histologic clues described here are very helpful.

**Thomas Krausz:** What a diagnostically challenging case! I managed to recognize "necrotizing lymphadenitis" but I needed your diagnostic clues to get to Kawasaki disease. Thanks John.

**Janez Lamovec:** Identical case with Dr. Berry's (AMR 9; case 1). Fortunately, a cover slip of my slide is still on.

**Thomas Mentzel:** Although skin biopsies in Kawasaki syndrome are performed infrequently only, in addition to unspecific features intraepidermal pustular lesions, subcorneal abscesses and focal endothelial necrosis have been reported in Kawasaki syndrome (Am J Dermatopathol 1988; 10: 218).

**Markku Miettinen:** Thank you for the scientific interpretation of this necrotizing lymph node, do not recall Kawasaki disease case.

**Elizabeth Montgomery:** As usual, Dr. Chan has shared a dazzling case. The fibrin thrombi seem a helpful feature in this example of Kawasaki disease.

**Santiago Ramon y Cajal:** Great case. Thank you.

**Juan Rosai:** Great case. I have never seen so much necrosis in Kawasaki disease, but then I do not think that I have recognized that entity more than once or twice in my life.

**Dominic Spagnolo:** Fabulous case of Kawasaki's necrotizing lymphadenitis - thanks John.

**James Strauchen:** Very nice case of mucocutaneous lymph node syndrome with an unusual abdominal presentation. In my experience, the lymph nodes are rarely biopsied.

**Saul Suster:** Thank you John for sharing this great example of a rare entity.

**Lawrence Weiss:** This case is indeed a beauty.

**Bruce Wenig:** Finally, a case I am able to diagnose after the previous cases! Thanks and thanks for the replacement of the long ago submitted case of Kawasaki disease by Gerald Berry.

#### **CASE NO. 5— CONTRIBUTED BY: DR. COLBY**

**Phil Allen:** Multiple small cystic lesions of the lung in a patient with von Hippel-Lindau's disease. These could be very easily missed at autopsy or even on biopsy. It may be more common than the negative literature findings would suggest.

**Carlos Bacchi:** This small cystic lesion does look like papillary cystadenoma. It is interesting to see the hamartomatous pattern in the remaining lung parenchyma. Thanks for the case and great discussion.

**David Ben-Dor:** This is obviously a provocative and stimulating case. Morphologically despite their clear nature the lesional cells don't look like renal cell carcinoma cells to me, and don't resemble cells otherwise regularly associated with pulmonary syndromes (though the staining properties clearly indicate lung provenance). I wonder, given that the nodule was stable over a period of three years (though this information isn't explicitly provided, one can speculate that the patient was also in stable condition), it was felt necessary to perform a lobectomy. Could an image guided needle biopsy or FNA have provided adequate information to at least rule out malignancy?

**Gerald Berry:** It looks hamartomatous. Given the association of VHL with a variety of neuroendocrine lesions would there be any thought to applying neuroendocrine markers to this case?

**Michele Bisceglia:** I could not recognize the "hilar" papillary cystadenoma (probably it is lacking in my section), but did see the microcysts with the papillary infoldings, which are scattered in the lung parenchyma and recall a very early phase of the endolymphatic sac papillary tumor (ELSPT) of the inner ear. Parenthetically we note here that 2 previous cases of ELSPT were previously circulated among the members of the Club: one was presented by Bruce Wenig in Seminar #19 (case 17) and the other (as an additional case) by Michele Bisceglia in Seminar #34; both these cases are currently in press in Adv Anat Pathol as selected cases for the section of AMR series.

**Ira Bleiweiss:** Very weird and a new one on me.

**John Chan:** This is a really difficult case. I had a hard time locating the lesion, and only after reading the description.

**Tom Colby:** My case – no new information or follow-up since I sent it in.

**Kum Cooper:** Thanks Tom for sharing this unique novel finding in the lung in a patient with vHL.

**Ivan Damjanov:** Difficult to classify from my slide, but I would agree with you.

**Otto Dietze:** Although I did not think of metastases, I have not seen this in the few personal observations of VHL before.

**Hugo Dominguez-Malagon:** Thank you for the case and illustrative discussion.

**Goran Elmberger:** Very interesting. Interstitial inflammation?? Wonder if lesions are hamartomatous or neoplastic. FISH test for LOH/deletion 3p25.5??

**Vincenzo Eusebi:** No lesion in my slide.

**Giovanni Falconieri:** Thanks Tom. Unfortunately I cannot be of any help. This case is very difficult, indeed.

**Christopher Fletcher:** Yet another astonishing and remarkably unique case. I have never personally seen anything with features such as this. In context, it would indeed seem most reasonable to regard these unusual lesions as hamartomatous.

**Jeronimo Forteza-Vila:** I see a cystic structure lined by epithelium and dilated vascular channels with hamartomatous characteristics, some of them remember me lymphangiectasias. I interpret like hamartomatous lung a cystic neighbourhood area.

**Masaharu Fukunaga:** Very interesting and unusual case! Tom. Thank you very much for sharing the case and the comments. I almost missed the lesions. I can have a good chance to study VHL.

**Thomas Krausz:** The pulmonary lesions are very interesting in this clinical context. If there is one than must be more, perhaps missed in the past. I will look out for them in the future.

**Markku Miettinen:** Agree on focal lymphoid infiltration and small cysts, thank you for linking this with VHL disease

**Elizabeth Montgomery:** Very cool. This case prompted me to see if we have any autopsies on file from VHL patients. We do [2]. The reports lack reports of interesting lung findings, but these may have been overlooked and the slides had disappeared from file.

When I checked into surgical specimens, none of the patients seemed to have lung resections. Your case begs the question as to whether these things are simply overlooked. Hopefully someone else in the group will look and stumble on more such cases.

**Santiago Ramon y Cajal:** Great case.

**Juan Rosai:** Great case of which I like to call the von Hippel –Lindau tumor. I am actually working on a small series of cases of this tumor with one of my fellows. One of them was located in the lung and pleura, and the patient developed a few months later multiple hemangioblastomas of the spinal cord.

**Dominic Spagnolo:** I have nothing to add Tom - seems indeed a unique finding in VHLD, and a hamartomatous nature would seem most likely. The resemblance of some areas to RCC are intriguing to say the least.

**James Strauchen:** Cystic clear cell hamartomatous proliferation apparently related to VHLD.

**Saul Suster:** Very interesting finding in VHL. I had never seen this before in the lung.

**Lawrence Weiss:** Very interesting case and very interesting syndrome.

**Bruce Wenig:** These pulmonary lesions have striking morphologic similarity to the endolymphatic sac papillary tumors that can be seen in association with van Hippel-Lindau disease.

#### **CASE NO. 6 — CONTRIBUTED BY: DR. DOMINGUEZ-MALAGON**

**Phil Allen:** Apparently solitary fibroleiomyomatous hamartoma of the lung in a female. This case seems to exhibit smooth muscle differentiation in the mesenchymal areas whereas I understand that the two cases reported by Saul and Cesar were purely fibroblastic. On the other hand the oestrogen and progesterone receptor stains are negative. I would still be inclined to check the uterus and to follow the patient in case more pulmonary lesions appear.

**Carlos Bacchi:** Thanks for showing this tumor (adenofibroma) in this rare location (lung). I totally agree with this diagnostic interpretation. The gross picture is spectacular!

**David Ben-Dor:** Pathology more typical of the breast or uterus but in the lung. At least the patient is a woman.

**Gerald Berry:** It looks like a variant of a pulmonary hamartoma. Nice case.

**Michele Bisceglia:** Pulmonary adenofibroma. Striking example. Thank you.

**Ira Bleiweiss:** Agree.

**John Chan:** I favor interpretation of pulmonary hamartoma. Like other mesenchymal lesions in the lung (such as solitary fibrous tumor), the entrapped epithelial component may produce a phyllodes pattern.

**Tom Colby:** Agree with diagnosis. The issue in a case like this is exactly what name to use. To me this is basically a hamartomatous lesion (although the atypia bothered me a little bit and I guess that's why we have words like "symplastic!").

**Kum Cooper:** Hugo, there certainly is a striking resemblance to phyllodes tumor and Mullerian adenofibroma! Thank you.

**Ivan Damjanov:** Agree.

**Otto Dietze:** Nice case, it is very suggestive of a hamartoma.

**Goran Elmberger:** Thanks for unusual case. Not seen in my 15 years at pulmonary service Karolinska.

**Vincenzo Eusebi:** Pulmonary adenofibroma.

**Giovanni Falconieri:** Agree with your assessment. No experience with the subject. Thanks for sharing with us this beautiful case.

**Cyril Fisher:** Pulmonary adenofibroma with striking 'phyllodes' architecture, thanks, Hugo.

**Christopher Fletcher:** A very convincing example of pulmonary adenofibroma – in lesions such as this, can we be sure that the epithelial component is actually neoplastic? Or could it be, as with pulmonary hamartomas, that it is the mesenchymal component which is neoplastic and the epithelial element is simply entrapped/distorted?

**Jeronimo Forteza-Vila:** I agree with the diagnosis, grossly it has a phyllodes appearance.



**Masaharu Fukunaga:** A very beautiful case, thank you, Hugo. The stroma seems to be smooth muscle (hamartomatous) for me.

**Thomas Krausz:** Never seen one before. Thank you for submitting it.

**Janez Lamovec:** Very similar to phyllodes tumor of the breast and one may doubt that epithelial structures are only entrapped pre-existent epithelium. With a huge size of this tumor some other "entrapped" formations could be expected.

**Thomas Mentzel:** Many thanks for sharing this extraordinary case of pulmonary adenofibroma.

**Michal Michal:** Does not have (did not) the patient leiomyomas of the uterus to exclude "benign metastasizing leiomyoma of the uterus"?

**Markku Miettinen:** The stromal element looks it could be smooth muscle; adenoleio-myomatous hamartoma sounds like a good name; this could actually be a smooth muscle neoplasm with secondary epithelial proliferation, similar to that in "pulmonary hamartoma", now understood a chondroid neoplasm.

**Santiago Ramon y Cajal:** I suppose that the tumor had similar features throughout all the mass and that there is not any other lesion outside lungs. It is worrisome because of the huge size.

**Juan Rosai:** It looks like a good example of so-called fibroleiomyomatous hamartoma, except for the fact that some of the lesions diagnosed as such have turned out to be metastases of smooth muscle tumors from the female genital tract or, less commonly, the GI tract (Am J Surg Pathol 3: 325, 1979).

**Dominic Spagnolo:** Have never encountered this adenofibromatous lesion of lung - thanks very much!

**James Strauchen:** Unusual pulmonary hamartoma resembling adenofibroma or phyllodes tumor.

**Saul Suster:** This case looks identical to the two cases we reported with Cesar Moran in Histopathology (Vol.23:547-551, 1993), except for the fact that this one is huge. The adenofibromatous, club-like papillary architecture is rather distinctive and one that I have not previously seen in other types of pulmonary hamartomas or in stromal tumors that "entrap" normal pulmonary parenchyma.

**Lawrence Weiss:** Probably a purely stromal proliferation?

**Bruce Wenig:** Nice case.

#### **CASE NO. 7 — CONTRIBUTED BY: DR. ELMBERGER**

**Phil Allen:** Low-grade, TTF-1 positive, nasopharyngeal papillary adenocarcinoma. I note that the youngest patient in Carrizo and Luna's paper in Annals of Diagnostic Pathology was only nine years. I have not read the study of 34 cases by Zong et al. in the Chinese Medical Journal but there were no recurrences or metastases after surgical excision in any of Bruce Wenig's nine cases. The role of radiotherapy also needs to be questioned. I think I have only seen sections of one of these before, which I suspect was the one published by Andrew van Hasselt and Ng Ho Keung from the Chinese University in Hong Kong (your reference 3). I don't know if that one recurred or metastasized. Thanks for the contribution.

**Carlos Bacchi:** Agree. Interesting discussion about TTF1!

**David Ben-Dor:** Welcome to the club, and thanks for this very provocative case. This lesion certainly looks innocuous and to me it has serous features. I wouldn't have thought it to be a malignant tumor. This entity isn't described (or at least not in detail) in either Prof. Rosai's textbook or in the most recent AFIP fascicle on the upper respiratory tract. However it is nicely illustrated in the recent WHO publication on head and neck tumors (chapter written by Bruce Wenig and John Chan, so the club has quite a bit of academic firepower for this very rare entity). A question I would like to raise is, given its extreme rarity with few published reports, and with the patients in the series reported in 1988 by Bruce Wenig et al showing no adverse outcome with follow up of up to 6 years, why call it carcinoma straight out? Even for the most intelligent parents who are capable of understanding that the lesion is very unusual and for the most part behaves well, it would be difficult to take with equanimity the fact that their young daughter has a condition for which the emotionally laden term "cancer" is used, even a very well behaving one.

**Gerald Berry:** Low grade papillary adenocarcinoma. I am disappointed (although not surprised) to hear of the diminishing specificity of TTF-1! I was not aware of the previous reports of TTF-1 positivity in this lesion. Thank you.

**Michele Bisceglia:** Nasopharyngeal papillary adenocarcinoma. Thank you for sharing this case with us and welcome to the Club. I did not know this type of tumor, which surely can be underestimated and go un-recognized. Your considerations on TTF-1 positive tumors are also interesting. The tumor you presented looks different from the tubulo-papillary low-grade sinonasal adenocarcinoma recently described by the Pilsen group (ref. 1. Skalova A, Cardesa A, Leivo I, Pfaltz M, Ryska A, Simpson R, Michal M. Sinonasal tubulopapillary low-grade adenocarcinoma. Histopathological, immunohistochemical and ultrastructural features of poorly recognized entity. Virchows

Arch 2003;443:152-8; ref. 2. Luna MA. Sinonasal tubulopapillary low-grade adenocarcinoma: a specific diagnosis or just another seromucous adenocarcinoma? Adv Anat Pathol 2005;12:109-15).

**Ira Bleiweiss:** OK, but why is this malignant?

**Tom Colby:** Agree with diagnosis. A new lesion for me.

**Kum Cooper:** Wow the third novel papillary lesion in a row. Welcome on board Goran! Was good to see you in Atlanta.

**Ivan Damjanov:** Agree.

**Otto Dietze:** Interesting case; several years ago I have seen a case of high-grade sinonasal adenocarcinoma positive for TTF1 and CK20.

**Hugo Dominguez-Malagon:** Beautiful case, it proves the un-specificity of so called specific antibodies such as TTF-1.

**Vincenzo Eusebi:** Well differentiated papillary nasopharyngeal carcinomas. TTF1 positivity was unexpected. Better to know.

**Giovanni Falconieri:** Excellent case. Thanks for contributing this challenging lesion. Very instructive. I am pleased to welcome you into the Club. I am pretty confident that your input shall reflect positively in the forum.

**Cyril Fisher:** Low-grade adenocarcinoma of nose. Thanks for interesting discussion especially about TTF-1 and welcome to the Seminar. This case can be compared with seminar 43 case 12 from Michal Michal.

**Christopher Fletcher:** A beautiful case which nicely confirms the unexpected findings described by Mario Luna in 2005. I think one can only speculate about the reason for the TTF-1 positivity in lesions of this type.

**Jeronimo Forteza-Vila:** Thanks for this interesting case. Taking in consideration the development, it would be adequate to call it Papillary Tumor.

**Masaharu Fukunaga:** Welcome to the Seminar, Dr. ElMBERGER. At first I consider it adenoma because of lack of atypia. Thank you very much for the comments, especially about the tumor markers.

**Thomas Krausz:** It is deceptively bland. Can they metastasize? I am glad you brought this entity to my attention.

**Janez Lamovec:** Epithelial uniformity, focal crowding and "heaping up" of cells, hyperchromatic nuclei and suggestive invasion are elements for the diagnosis of low-grade adenocarcinoma. I've never seen this tumor before. Thank you.

**Thomas Mentzel:** An interesting case of nasopharyngeal papillary adenocarcinoma arising in a very young patient. Thanks for discussing the limitations of TTF1 stainings in the differential diagnosis of adenocarcinomas, and as with other "specific markers" also TTF1 can be used in the right context only.

**Markku Miettinen:** Agree on papillary carcinoma, striking similarity with thyroid ones, ectopic thyroid papillary ca? but alternative explanations such as yours are very reasonable, even considering TTF1+.

**Elizabeth Montgomery:** What an excellent case, particularly as it offers the opportunity to learn that the reactive TTF is a potential pitfall. One of my colleagues who handles both lung and head and neck cases tells me he performs many TTFs for interest and has not encountered specificity problems. One wonders if different antibodies offer different specificity profiles.

**Santiago Ramon y Cajal:** Agree although I think would be interesting to study other molecular thyroidal markers.

**Juan Rosai:** Great case of papillary adenocarcinoma. From a morphologic standpoint, it would be hard to tell this apart from a metastatic carcinoma arising from the thyroid or the lung, but I guess this has been taken care of with the immunohistochemical evaluation.

**Dominic Spagnolo:** Welcome to the club Goran, and thank you for this stunning example of low-grade nasopharyngeal papillary carcinoma. The TTF-1 positivity is intriguing and I like your proposed explanation for this.

**James Strauchen:** Low-grade papillary adenocarcinoma of the nasopharynx. TTF-1 is a surprise.

**Saul Suster:** Thank you Goran for this interesting and educational case, and welcome to the Club!

**Lawrence Weiss:** Interesting neoplasm that I have never seen before. It's another example that no one immuno is a definitive immuno of anything.

**Bruce Wenig:** Low-grade nasopharyngeal papillary adenocarcinoma; I have previously seen this case. Thanks Goran.

**CASE NO. 8 — CONTRIBUTED BY: DR. FALCONIERI**

**Phil Allen:** Undiagnosed histologically indeterminate myxoid tumor with multinucleate stromal cells, amianthoid-like fibres and peripheral lympho-plasmocytic reaction, ? unusual variant of inflammatory myofibroblastic tumor, lung. I don't know what this is either, Falco. It looks as though it is a primary and it could be benign.

**Carlos Bacchi:** No idea about the diagnosis. I believe that is benign. Looking forward to hearing other members' diagnostic opinion.

**David Ben-Dor:** Is there enough inflammation to consider inflammatory myofibroblastic tumor? No specific mention of whether staining for ALK was performed is given.

**Gerald Berry:** I have not previously seen such a myxoid background in inflammatory myofibroblastic tumor but it appears to be the best category to place it in.

**Michele Bisceglia:** Agree. My favourite diagnosis is "inflammatory myofibroblastic tumor" in this case.

**Ira Bleiweiss:** Sarcoma NOS???

**John Chan:** Difficult to give it a name. Perhaps inflammatory myofibroblastic tumor? This is certainly unusual because the tumor cells and the inflammatory component are segregated. There is in fact some morphologic resemblance to inflammatory myofibroblastic (fibromyxoid) tumor of the urinary bladder in some areas.

**Tom Colby:** Agree with observations and discussion. Sarcomatoid carcinoma is always in the differential with this degree of atypia. Negative epithelial markers does not absolutely exclude that possibility. The paucity of mitotic figures would be unusual for sarcomatoid carcinoma. I like the idea of inflammatory fibrosarcoma arising in a background showing some features of IMFT.

**Kum Cooper:** Sarcomatoid carcinoma or pulmonary blastoma (with muscle differentiation) even though I do not see any epithelial elements. Sorry Falco not much help.

**Ivan Damjanov:** To me this looks like a cartilage producing tumor and I would call it chondrosarcoma.

**Otto Dietze:** Perhaps a myofibroblastic tumor of a peribronchial lymph node?

**Hugo Dominguez-Malagon:** There is chondroid matrix in some areas, I would add to the possibilities a myoepithelial tumor.

**Vincenzo Eusebi:** Myofibroblastic tumor seems appropriate to me in view of immuno results and myxoid appearance.

**Cyril Fisher:** Based on the pleomorphism, mitoses and actin positivity, I considered low grade myofibroblastic sarcoma but the amianthoid fibers are exceptional although they have been described in a variety of situations.

**Christopher Fletcher:** I do not know how to classify this lesion – the fact that the bulk of the inflammation is at the periphery of the tumor cell nodules, rather than being admixed with the tumor cells, makes inflammatory myofibroblastic tumor unlikely. The appearances do not seem to fit neatly into any well-recognized category. The focally more epithelioid and clustered morphology, as well as the rather hyaline matrix might make one think of a myoepithelial neoplasm, but your results of immunostaining do not seem to support this. I suppose that one would be left saying something descriptive like "atypical spindle cell neoplasm best regarded as low grade sarcoma". It will be interesting to hear how this tumor behaves.

**Jeronimo Forteza-Vila:** It reminds us of a pseudoinflammatory tumor, but the mesenchymal component atypia attract our attention.

**Masaharu Fukunaga:** I like this case. Thank you Falco. I would call it inflammatory myofibroblastic tumor (inflammatory pseudotumor)

**Thomas Krausz:** I also find it difficult to classify. It could be myoepithelial. I would try a variety of keratins and myoepithelial markers. Also, see publication by Pelosi et al in AJSP March 2006 entitled "Salivary gland-type tumors with myoepithelial differentiation arising in pulmonary hamartoma".

**Janez Lamovec:** This appears as a myofibroblastic/myoid lesion to me, with some suggestive palisading of cells peripherally and (in my slide) vague hyaline/fibrillary aggregates; the lesion at least focally somewhat resembles palisaded myofibroblastoma but is, of course, not in a lymph node. Peculiar lesion.

**Thomas Mentzel:** A very difficult case indeed. Probably the descriptive term of unusual myofibroblastic tumor with inflammation and amianthoid fibres would be the best. I've seen recently (in a small biopsy only) a solitary myofibroblastic neoplasm arising in the lung and showing identical features to intranodal myofibroblastoma with amianthoid fibres.

**Michal Michal:** Can "metastatic" heart myxoma be excluded clinically?

**Markku Miettinen:** Unusual morphology, difficult to connect with inflammatory myofibroblastic tumor. Apparently you ruled out metaplastic carcinoma; a metastasis of sarcomatoid Ca or sarcoma could be a consideration also.

**Elizabeth Montgomery:** The lesion has an inflammatory cuff reminiscent of a gastric schwannoma [noted that S100 is negative]. The chondroid backdrop, vacuoles, and nuclear cytology made me consider epithelioid hemangiothelioma but apparently CD31 and CD34 are negative. Occasionally hamartomas can display elements that appear immature but I have no experience with such cases. Would expect this to behave indolently, whatever it is!

**Santiago Ramon y Cajal:** I would include in the differential a low-grade fibromyxoid sarcoma (metastases).

**Juan Rosai:** I am not sure about the nature of this case, but I would go along with Dr. Falconieri's suggestion that it represents an inflammatory pseudotumor with a very prominent myxoid change. The inflammatory infiltrate is rather pronounced and the non-lymphoid cells have an appearance which is morphologically and immunohistochemically consistent with myofibroblasts. At least one case interpreted as the myxoid variant of inflammatory pseudotumor is on record (Cancer 54: 861-865, 1984).

**Dominic Spagnolo:** I don't have an answer for this unusual myxoid lesion. I guess it is most likely a low-grade inflammatory myxoid sarcoma, NOS, or inflammatory myofibroblastic tumor, but I am concerned about the complete lack of mitoses in my section. Has metastatic GIST been excluded?

**James Strauchen:** No idea! The lymphoplasmacytic reaction is reminiscent of an inflammatory myofibroblastic tumor. I did not find amianthoid fibers. Did you try ALK-1?

**Saul Suster:** I do not think this represents an "inflammatory myofibroblastic tumor". Such tumors usually have irregular infiltrating borders, prominent desmoplastic stromal response, and an even distribution of the inflammatory elements throughout the lesion rather than concentrated in the periphery. In a case like this, I would try to pursue a more detailed clinical history to rule out first the possibility of a metastasis from a soft tissue sarcoma, such as an extraskeletal myxoid chondrosarcoma or other type of myxoid sarcoma.

**Lawrence Weiss:** Have EBV and ALK been done? Nothing better than low-grade inflammatory fibrosarcoma.

**Bruce Wenig:** I agree with a myofibroblastic dominant lesion/proliferation that may well "fit" into the spectrum of an inflammatory (myofibroblastic) pseudotumor. It may be worthwhile, if not already done, to do ALK-1 staining although the overall features of this lesion are not quite like the inflammatory myofibroblastic tumors that I have seen previously.

#### **CASE NO. 9 — CONTRIBUTED BY: DR. FOLPE**

**Phil Allen:** Liver metastasis of a testicular germ cell tumor now differentiating only as primitive neuroectodermal tumor resembling medulloepithelioma. Some of the tumor also resembles a neuroendocrine carcinoma. Thanks for the contribution.

**Carlos Bacchi:** Great case Andrew. This case does show overlapping morphology with medulloepithelioma.

**David Ben-Dor:** Morphologically the tumor has endometrioid/sertoliform features (to me). Was anything like this seen in the previous tumor?

**Gerald Berry:** Looks like high-grade malignant neoplasm with neuroendocrine differentiation arising in the setting of a germ cell tumor. PNET looks like a good fit.

**Michele Bisceglia:** Agree. Nice presentation. You rightly underlined that this PNET which is related to a testicular germ cell tumor is different from what we usually call "peripheral PNET". Since gonadal PNET are indeed central PNET at least histogenetically, this tumor is an "ectopic" "central PNET", since as a central PNET it is located outside the (normal) neuraxis.

**Ira Bleiweiss:** Agree.

**John Chan:** On casual examination, I dismissed the hepatoid component as merely the solid/poorly differentiated component of serous carcinoma. The arguments in favor of a hepatoid carcinoma are certainly convincing.

**Tom Colby:** Spectacular case. Thanks for sharing it.

**Kum Cooper:** Thanks Andrew. We saw a similar case with a testicular germ cell tumor in the early 90s (mixed germ cell components; No PNET component; then with retroperitoneal metastases in the mid 90s (pure PNET; NO germ cell components); then with bone marrow metastases in 2005 (with pure PNET). Strong CD 99 positive and pure PNET with no glandular structures nor germ cell components.

**Ivan Damjanov:** Agree with your interpretation. Never seen one arising in a germ cell tumor. Could some of that be ependymal ?

**Otto Dietze:** Without clinical information I think that it is difficult to distinguish it from neuroendocrine carcinoma.

**Hugo Dominguez-Malagon:** Agree with the diagnosis, somatic transformation of GCT is a rare phenomenon that causes diagnostic confusion, and changes the therapeutic approach.

**Goran Elmberger:** Very interesting case. These germ cell tumors are really like a Pandora's box. The more sections you block in the primary setting the more patterns you may see. Sometimes the metastatic presentation and the selective pressure of therapy nicely isolates resistant clones such as this.

**Vincenzo Eusebi:** Very nice case. Thank you.

**Giovanni Falconieri:** Gorgeous case, Andrew. Thanks for this valuable contribution and the excellent discussion.

**Cyril Fisher:** Metastatic primitive neural tumor, very unusual site of metastasis. As you indicate, the terminology can cause confusion with that of primary soft tissue tumors. Presumably this is CD99 negative? Some of the cases in Michael's paper were positive for HBA71 (a CD99 antibody). Perhaps the term neuroectodermal should be reserved for those.

**Christopher Fletcher:** A very beautiful and entirely convincing case – I have only seen one or two such lesions in the past. I agree with you, particularly when dealing with the oncologist, that it is important to make clear that lesions such as this bear no relationship to Ewing's/PNET.

**Jeronimo Forteza-Vila:** I agree with the diagnosis. Thanks for so interesting case.

**Masaharu Fukunaga:** Immature neuroectoderm elements of the immature teratoma of the testis. A very beautiful case. Thank you, Andrew for sharing the case.

**Thomas Krausz:** Agree with diagnosis. In places it looks ependymal/ependymoblastic.

**Janez Lamovec:** Metastatic medulloblastoma. What a case!

**Thomas Mentzel:** Many thanks Andrew for sharing this spectacular case.

**Markku Miettinen:** Agree on neuroendocrine carcinoma; origin from a germ cell tumor is very plausible if other possibilities have been ruled out.

**Elizabeth Montgomery:** Thanks so much for this educational case.

**Santiago Ramon y Cajal:** Great case.

**Juan Rosai:** Very nice example of peripheral neuroepithelioma arising within the context of a malignant germ cell tumor, with beautiful demonstration of so-called Flexner rosettes. It reminded me of the classical article on the subject by Aguirre and Scully (Arch Pathol 107: 643-645, 1983).

**Dominic Spagnolo:** This is the second such case I have encountered of PNET-like tumor in association with testicular germ cell neoplasia. The first was unfortunately diagnosed in a close family member. He developed a PNET-like metastasis with divergent differentiation in a cervical node/soft tissue 10 years after treatment for testicular germ cell neoplasia. There was no PNET-like component in his primary. He succumbed within a year after intensive chemotherapy (?? and radiotherapy). Thanks for the case Andrew.

**James Strauchen:** Metastatic germ cell tumor with predominant neuroepithelial differentiation (PNET).

**Saul Suster:** Very rare presentation. Thank you for contributing this unusual case.

**Lawrence Weiss:** So what you are telling us is that there are PNET's and then there are PNET's. Great case. We have to be a neuropathologist sometimes to sign out germ cell tumors.

**Bruce Wenig:** Cool case (not for the patient).

#### **CASE NO. 10 — CONTRIBUTED BY: DR. FUKUNAGA**

**Phil Allen:** Metastatic omental serous carcinoma with hepatocellular component from a primary in the left fallopian tube. I assume that the left ovary was not involved.

**Carlos Bacchi:** Very convincing case of hepatoid carcinoma with serous component arising in an unusual location (fallopian tube).

**David Ben-Dor:** Another interesting gynecological tumor from Masaharu. From the architectural point of view the papillae and slit like glands look serous, but cytologically less so. To be honest looking at the slide without prompting I wouldn't consider the possibility of a hepatoid tumor – the solid areas show sheet like growth and the cells are either clear or show weakly eosinophilic cytoplasm; in my view the cells forming the slit like glands and papillae have nuclear features similar to those in the solid areas, and hepatic tumors are typically non papillary and non glandular. But I can't argue with the immunohistochemistry. In my book you deserve a lot of credit for thinking of the possibility and having the appropriate studies performed- I wouldn't have done so based on the H&E. Maybe in this era descriptive terms such as "hepatoid" will be used based on immunohistochemical properties and not just on morphologic similarities.

**Gerald Berry:** High-grade carcinoma with hepatoid component. Agree. Nice example.

**Michele Bisceglia:** Hepatoid carcinoma with serous component of the Fallopian tube. Very rare and beautiful case. Primary tubal carcinomas are absolutely rare but most often interesting. Just few days ago I have seen a case of poorly differentiated primary tubal carcinoma with combined areas of serous carcinoma and lymphoepithelial carcinoma (with diffuse expression of p53 in both areas).

**Ira Bleiweiss:** Agree.

**Tom Colby:** Agree with diagnosis.

**Kum Cooper:** Lovely case Masa, and great support both with IHC and clinically. We saw a case recently that involved the ovary and the omentum. It was also HEPAR-1+ and CD10/pCEA+ highlighting the ductular differentiation. It even had bile production and grossly showed a green tinge in color. We sent it to a GYN expert who insisted that it was a metastatic hepatocellular carcinoma (which we had clearly ruled out with both MRI and CT scans!).

**Ivan Damjanov:** Hepatoid carcinoma, agree.

**Otto Dietze:** Excellent case and presentation!

**Hugo Dominguez-Malagon:** Extraordinary case of hepatoid carcinoma of fallopian tube, thank you.

**Goran Elmberger:** Great case. I must admit I initially favored YST but your discussion as well as epidemiological situation, component of serous carcinoma and absence of specific morphological structures of YST convinced me of your diagnosis.

**Vincenzo Eusebi:** The immuno is indicative of hepatic differentiation. Hepatoid carcinoma on this slide would have not been my immediate diagnosis.

**Giovanni Falconieri:** Another extraordinary contribution. Thanks for this submission and the thorough discussion.

**Cyril Fisher:** Hepatoid carcinoma, very nice case.

**Christopher Fletcher:** Very convincing example of hepatoid carcinoma arising in a remarkably unusual clinical setting.

**Jerónimo Forteza-Vila:** I agree with the diagnosis. Thanks for so interesting case.

**Thomas Krausz:** Agree with diagnosis. Great case. Immuno is very helpful. I have seen rare examples before in the ovary.

**Thomas Mentzel:** Many thanks for this unusual case.

**Michal Michal:** It all seems to me as malignant germ cell tumor.

**Markku Miettinen:** Solid poorly differentiated carcinoma, agree with your interpretation on hepatoid differentiation, with HEPAR and CEA-positivity.

**Elizabeth Montgomery:** This is an amazing case.

**Juan Rosai:** Great demonstration of hepatoid carcinoma admixed with a serous pattern indicative of mullerian derivation. It sounds from the description like the tumor may have arisen from the fallopian tube. It is of interest to see how the fallopian tube, which was ignored for so many years by gynecologic pathologists, is now coming into the front line. I was reading the other day that, according to some authors, a high proportion of tumors that we traditionally regarded of primary ovarian origin are really ovarian extension of fallopian tube carcinomas. I also thought of interest the fact that in one of the electronmicrographs there is a tumor cell nucleus with the kind of nucleolus one sees in germ cell tumors, particularly seminomas and dysgerminomas, characterized by a prominent dispersed nucleolonema and a dispersed pars amorpha.

**Elvio Silva:** I probably missed several cases like this one. I would have signed this out as high-grade Mullerian Ca with different patterns, but I agree with your diagnosis.

**Dominic Spagnolo:** Thank you Masa for this wonderful case of hepatoid carcinoma of the fallopian tube. Have not encountered one before.

**James Strauchen:** I favored a hepatoid yolk sac tumor but your explanation is equally tenable.

**Lawrence Weiss:** Great case. Completely agree.

**Bruce Wenig:** Yup, as Maxwell Smart would say "the old hepatoid carcinoma with serous component of the fallopian tube".

#### **CASE NO. 11 — CONTRIBUTED BY: DR. KRAUSZ**

**Phil Allen:** Ligneous vaginitis associated with adenosis. I missed it again! I well remember Harold Fox presenting a case of ligneous cervicitis at a USCAP evening gyne specialty conference some 10 or 15 years ago. He took great pleasure in pointing out that the condition was not mentioned in the standard American gynecological textbooks at that time, but was well described in an English text. It's good to see Thomas re-presenting and updating Harold's disease in the Queen's 80<sup>th</sup> year.

**Carlos Bacchi:** Incredible case with great clinicopathological correlation. Amazing how the morphological recognition of a particular lesion (in this case subepithelial deposition of fibrin) can be crucial in helping the patient.

**David Ben-Dor:** Cases showing deposits of "amorphous" material are certainly common and I agree, wouldn't attract much attention from most pathologists (including myself) as far as determining its exact nature (except maybe for ruling out amyloid). This case and Thomas' careful explanation put this problem in a new light, as it demonstrates that in some instances an otherwise seemingly nondescript finding can be part of a progressive systemic condition with definite implications for the patient but which is treatable if properly diagnosed. Thus a condition which would have been considered a curiosity in the past has morphed into something which bears attention. Definitely food for thought.

**Gerald Berry:** The term "ligneous vaginitis" is a new one to me. Raising the possibility of hypoplasminogenemia is a stroke of genius!! Beautiful case.

**Michele Bisceglia:** Ligneous vaginitis in association with adenosis. Very interesting discussion. Thank you, Thomas. By the way another similar case ("ligneous cervicitis") was previously circulated by SJ Schnitt in Seminar #28 (case 17).

**Ira Bleiweiss:** Another new one.

**John Chan:** A brilliant work-up! The various types of ligneous inflammatory lesions are always elusive to me.

**Tom Colby:** New lesion for me. I like esoterica like this, particularly when it has terms like "ligneous" in the diagnosis.

**Kum Cooper:** Thanks Thomas. I recall a ligneous cervicitis submitted to the club many years ago. Great write-up and great education! PS, I checked Michele's magnificent work on categorizing past cases....and yes it is there AMR Seminar #28, case 17 submitted by Stuart Schnitt (I forgot that he was once a member!!).

**Ivan Damjanov:** Unusual, but has all the features of the conjunctival lesion.

**Otto Dietze:** To my opinion a really difficult diagnosis, if only a small biopsy is available.

**Hugo Dominguez-Malagon:** Ligneous vaginitis!, incredible case, never heard of it.

**Goran Elmberger:** That's a wonderful pick-up diagnoses. Highly interesting and also quite impressive how fast medical knowledge and understanding has advanced since my edition (4; 1994) of Blausteins Pathology of the Female Genital Tract ed Kurman. Need to update my library!

**Vincenzo Eusebi:** Thank you very much for this case. I did not know this condition.

**Giovanni Falconieri:** Great case, Thomas. I agree with everything. I have already seen a few examples of the condition in both the location. Still wondering about the choice and appropriateness of the "woody" appellation. No question that the lesion can be overlooked.

**Cyril Fisher:** Ligneous vaginitis with adenosis, extraordinary case, thanks, Thomas.

**Christopher Fletcher:** This is a very educational case and I have no doubt that I would have missed the significance of this hyaline material – most likely attributing it to mucosal ulceration. Many thanks indeed!

**Jeronimo Forteza-Vila:** We haven't experience about this localization of the disease. The existence of a mouse model have connection with this entity it's especially interesting.

**Masaharu Fukunaga:** Thank you very much for the beautiful case, Thomas. Ligneous vaginitis. I have never seen this lesion before.

**Janez Lamovec:** Ligneous vaginitis and adenosis. A case of this lesion in the cervix was submitted to AMR slide seminar some time ago (AMR 28, case 17 – Dr. Schnitt). Instructive discussion.

**Thomas Mentzel:** Many thanks Thomas, and to be honest I haven't seen (or missed) this condition until now.

**Markku Miettinen:** Pseudomembranous ulcerative lesion w/ squamous metaplasia, your description and designation "ligneous" sound good. Adenosis in my slide was quite mild.

**Elizabeth Montgomery:** You are so clever. Ligneous vaginitis. Never heard of it. Ligneous conjunctivitis. Never heard of that either. I would have never noticed the key findings had you not explained the patient's plasminogen deficit. Now I will over diagnose this weekly on every ulcer with apparent hyalinized fibrin. Ligneous esophagogastritis, ligneous proctitis. Ligneous decubitus ulcer. Cannot wait. Thanks for the education.

**Juan Rosai:** I must confess I would have diagnosed this case simply as vaginal adenosis of the tubo-endometrial type associated with fibrosis and hyalinization, but after reading the scholarly comments by Dr. Krausz, I think he makes a very good point for the existence of what I gather must be regarded as a new entity in this location.

**Dominic Spagnolo:** Wow! What an amazing case of ligneous vaginitis and adenosis. Thanks for slide and the detailed discussion Thomas - was not aware of the hypoplasminogenemia story.

**James Strauchen:** I missed the ligneous change entirely, considering the fibrinous deposits secondary to the prior surgery. The relation to plasminogen deficiency is fascinating and makes sense pathophysiologically.

**Saul Suster:** You are to be commended for this diagnosis! The association of this subtle finding with hypoplasminogenemia is stunning. Dr. Stuart Schnitt also submitted a similar case to the club a few years ago.

**Lawrence Weiss:** I am learning whole new areas of medicine. I never heard of ligneous conjunctivitis, let alone vaginitis.

**Bruce Wenig:** Looked benign to me but I wasn't sure what to call it until reading Thomas's comments. Thanks.

#### **CASE NO. 12 — CONTRIBUTED BY: DR. MENTZEL**

**Phil Allen:** Progressive nodular histiocytomas with hundreds of lesions, excision biopsies from each forearm. This is the first case I have seen, and I have been on the lookout for it for about 20 years. Thanks very much for the contribution.

**Carlos Bacchi:** Agree with the histological diagnosis. Amazing clinical history!

**David Ben-Dor:** At least for the larger of the two lesions (seen in slide 12a), I find the atypia and cellularity very worrisome. When I first saw the slide I thought it was melanoma. The lesion in slide B though looks tamer. I would be very hard pressed to argue this diagnosis given the clinical history of recurrent lesions going on 16 years at this point. A lesion looking like this and positive for S100 to boot, give me a break!!

**Gerald Berry:** Agree although dermal lesions that come in numbers of 2 or more always cause me added concern.

**Michele Bisceglia:** I would have qualified both tumors as benign fibrous histiocytoma of the skin. However, given the clinical picture, the diagnosis of "progressive nodular histiocytoma" I think is appropriate.

**Ira Bleiweiss:** DFS to me.

**John Chan:** These two skin lesions alone look like conventional dermatofibroma only. Difficult to link this with the various non-Langerhans cell histiocytosis syndromes.

**Tom Colby:** Progressive nodular histiocytoma sounds descriptively appropriate. I think there is a lot about histiocytic lesions that we have yet to learn and this may be one such example. Another is Erdheim-Chester disease.

**Kum Cooper:** Thanks Thomas. I was wondering what the "catch" was until I read the clinical picture!

**Ivan Damjanov:** I have nothing to add—no experience with similar lesions.

**Otto Dietze:** I was not aware of this before, thank you.

**Hugo Dominguez-Malagon:** Fits very well with progressive nodular histiocytoma.



**Goran Elmberger:** Interesting and rare case. I have nothing against the suggested diagnosis but I am surely not an expert on skin pathology. Looks slightly aggressive to me with regard to cellularity, mitoses and ulceration. Part of spectrum?

**Vincenzo Eusebi:** Thank you very much for this case.

**Giovanni Falconieri:** Microscopically, this does not appear a terrific challenge. However, I would have had a hard time in placing things in the exact clinical context. Thanks Thomas for this interesting contribution.

**Cyril Fisher:** Looks like a cutaneous (fibro)histiocytic lesion, clinically consistent with progressive nodular histiocytoma.

**Christopher Fletcher:** I think that both of these lesions have more histiocytoid cytomorphology than one would expect in a usual dermatofibroma/fibrous histiocytoma – and, indeed, it therefore seems more logical to regard these lesions as an unusual multifocal proliferation of true histiocytic cells of some type. I do not believe that there is any convincing relationship between dermatofibroma and lesions such as xanthogranuloma or reticulohistocytoma. There seem to be a large number of cutaneous “histiocytic” lesions which are very difficult to classify in any reproducible way. Most of the literature regarding lesions of this type has been (and remains) very confusing, at least to me. Many thanks for sharing this impressive and unusual case.

**Jeronimo Forteza-Vila** The histology and the immunohistochemistry are concordant with a non aggressive histiocytic proliferation, even though S-100 positivity, the CD1a negativity and the absence of Birbeck bodies at the EM level don't make a connection with Langerhans cell histiocytosis. We haven't any previous experience with progressive nodular histiocytosis clinically but it would be a good diagnostic option.

**Masaharu Fukunaga:** Dermatofibroma with erosion. “Progressive nodular histiocytoma” is very new to me. Thank you very much for the unusual skin tumor.

**Thomas Krausz:** Histologically they look like variants of cellular fibrous histiocytoma. In this clinical context, I agree, progressive nodular histiocytosis is the most likely.

**Markku Miettinen:** Seems to be an odd syndrome, by clinical history. Initially considered cytologically “mild” AFX; would suggest additional evaluation of true histiocytic differentiation with CD163 antibody; the cell type looks more mesenchymal than truly histiocytic. Additional studies for CD21, other reticulum cell markers?

**Elizabeth Montgomery:** Nice case. Thanks for sharing it.

**Juan Rosai:** Nice case of dermatofibroma. As pointed out by Dr. Mentzel, the case is more interesting from a clinical than a pathologic standpoint because of the multiplicity of the lesions.

**Dominic Spagnolo:** A fascinating case, the clinical setting of which would seem to fit precisely with progressive nodular histiocytosis. Some of the histiocytes in biopsy II seem to be ingesting collagen/elastin. Is there any suggestion of an underlying myeloproliferative disorder??

**James Strauchen:** I was unaware of progressive nodular histiocytoma as a syndrome but the name seems apt as the lesions certainly resemble multiple dermatofibromas complete with overlying epidermal hyperplasia. Are these factor XIIIa positive?

**Saul Suster:** Was not aware of this clinical syndrome. Histologically looks like a cellular dermatofibroma. Thank you for educating me.

**Lawrence Weiss:** Factor XIII staining?

**Bruce Wenig:** Looked like a benign fibrohistiocytic proliferation.

#### **CASE NO. 13 — CONTRIBUTED BY: DR. MONTGOMERY**

**Phil Allen:** Inflammatory fibroid polyp, transverse colon. I'm sure I also would have failed to make the diagnosis on a small endoscopic biopsy. It's good to see that our Founder has written on this entity in the small intestine.

**Carlos Bacchi:** Thank you for the nice example of inflammatory fibroid polyp.

**David Ben-Dor:** I get to see these now and then in the stomach, I didn't know they can appear in the colon. Good to know if such a case turns up.

**Gerald Berry:** A remarkably large inflammatory fibroid polyp to have caused obstruction. Beautiful example.

**Michele Bisceglia:** Inflammatory fibroid polyp of the small bowel. Have seen a case with the same dramatic clinical presentation (bowel intussusception).

**Ira Bleiweiss:** Agree.

**Tom Colby:** Agree with diagnosis.

**Kum Cooper:** Thank you Elizabeth. I have only seen smaller examples of this fascinating polyp and never with obstruction either. I have found the CD 34 to be useful in small biopsies.

**Ivan Damjanov:** Agree. Nice Case.

**Otto Dietze:** Typical example and nice review of this entity.

**Goran Elmberger:** Interesting case and great review of literature. Peculiar perivascular oedematous change! Eosinophils just markers of subacute inflammation?

**Vincenzo Eusebi:** Inflammatory fibroid polyp.

**Giovanni Falconieri:** I agree, lovely example of IFP. Thanks for this contribution and the excellent update.

**Cyril Fisher:** Beautiful example of inflammatory fibroid polyp, thanks, Lizzie.

**Christopher Fletcher:** Beautiful example of inflammatory fibroid polyp – in my experience, these lesions seem to be notably more common in the small intestine, rather than the stomach, and I have noticed that the literature is confusing in this regard.

**Jeronimo Forteza-Vila:** I agree with the diagnosis.

**Masaharu Fukunaga:** A beautiful and florid case with an unusual clinical presentation. Thank you very much, Elizabeth.

**Thomas Krausz:** Fantastic example. The overlying mucosal/epithelial changes are also diagnostically challenging.

**Janez Lamovec:** We only saw this lesion in the stomach occasionally but never in other segments of gastrointestinal tract. A case of pigmented chromophobe renal carcinoma associated with angiomyolipoma that I submitted to AMR slide seminars some time ago was also associated with Vanek's tumor of the stomach.

**Thomas Mentzel:** Thanks for this beautiful example of inflammatory fibroid polyp of the colon. Only a brief "historical note" - granuloblastoma of the stomach has been regarded also as a pseudotumorous variant of fibrous histiocytoma in the past (Pathol Res Pract 1981; 171: 336-344).

**Michal Michal:** Dr. Vanek, who first described the tumor was the chairman of our Department of Pathology in Plzen for more than 25 years (*Daum O., Hes O., Vanecek T, Sima R, Zamecnik M, Mukensabl P., Hadravska S, Curik R, Michal M.: Vanek's tumor (Inflammatory fibroid polyp). Report of 18 cases. Comparison with 3 cases of original Vanek's series. Ann Diagn Pathol 2003;7: 337-347*).

**Markku Miettinen:** Very nice example of inflammatory fibroid polyp; looks similar to the ones in small intestine; they seem to be quite rare in the colon. In our experience on immunostains of about 60 small intestinal tumors of this type, they are almost uniformly CD34-negative.

**Juan Rosai:** Very nice case of inflammatory fibroid polyp, the first that I have seen in the large bowel. The onion-skin appearance of the fibroblasts around the vessels is particularly well-developed. It is interesting to note that in the past some of these lesions were called eosinophilic granulomas and that others were included into the category of hemangiopericytoma.

**Dominic Spagnolo:** Nice example of inflammatory fibroid polyp. Thanks.

**James Strauchen:** Inflammatory fibroid polyp. Very nice example.

**Lawrence Weiss:** Nice case.

**Bruce Wenig:** Nice case, Liz.

#### **CASE NO. 14 — CONTRIBUTED BY: DR. RAMON Y CAJAL**

**Phil Allen:** Autolytic liver with severe cholestasis and high-grade angiosarcomatosis of veins near the liver hilum and in pulmonary blood vessels, with respiratory insufficiency. I don't think the primary tumor is present in my section. To me, it looks more like a high-grade angiosarcoma than an epithelioid hemangioendothelioma.

**Carlos Bacchi:** Could this be an intravascular form of angiosarcoma?

**David Ben-Dor:** The intravenous disseminated tumor cells are impressive. Morphologically it would be tempting to call them "signet ring cells"; they also have plasmacytoid characteristics. Besides the intravenous disseminating component I couldn't find representation of the tumor mass itself and I didn't clearly see tumor cells in the sinusoids (maybe they were masked by post mortem artifact). The bile ducts look strange- reactive changes?

**Gerald Berry:** We seem to be seeing increasing numbers of aggressive vascular neoplasms these days (both hemangioendothelioma and angiosarcoma). The degree of intravascular extension is very impressive.

**Michele Bisceglia:** Epithelioid hemangioendothelioma with prominent intravascular dissemination. Agree with your diagnosis. Certainly the intravascular dissemination in your case is striking. By the way, in the interval between the time I looked at the slides of this Seminar and the time I am writing my comments (around 2 weeks' interval time), "believe it or not" a small/fine needle biopsy was performed here on a young female patient with 2-3 hepatic nodular lesions each sized 3-4 cm. The lesion has been signed out as consistent with "epithelioid hemangioendothelioma" (myxohyaline stromal background with spindle and epithelioid vacuolated cells which resulted positive for endothelial markers). Santiago, you asked for comments: here are some. From the description you gave, or in other words from the findings you discovered at autopsy, one cannot understand if the tumor arose in the liver or it arose in the lung. And in fact from the data of the literature, in some cases, multicentric and multifocal forms are very difficult to differentiate from metastatic spread from a single source as it seems to be in your case (you stated no liver mass on CT scan). Likely it arose from/around one of the large- or middle-sized vessels you described. According to the new WHO book on soft tissue tumors epithelioid hemangioendothelioma is an intermediate grade malignant tumor. From the data of the literature the range of metastatic rate is around 10-30% with classic histologies correlating with the lower end of the rate and atypical histologies correlating with the upper end. High-grade angiosarcomatous transformation of a case of epithelioid hemangioendothelioma was presented in abstract form in the Italian journal *Pathologica* 3 years ago (and as far as I know it was the first and still is the only one on record) (Bisceglia et al. *Emangioendoteliooma maligno della cute con metastasi linfonodali di angiosarcoma epitelioido*. Osservazione di un caso: studio oistologico, immunohistochimico e ultrastrutturale. *Pathologic a*2003;95:367 – abstract). This tumor arose 10 years before in the skin of a 20-yo male patient, and was (elsewhere) interpreted as a melanoma (with confirmation by a melanoma expert in a referral non-Italian Center). It recurred as axillary lymph node metastasis, which was interpreted as metastatic melanoma (diagnosis made elsewhere, but in a different place from the one where the 1<sup>st</sup> diagnosis was established). After that I had the opportunity to look at both the primary and the metastatic tumor: the primary skin tumor was epithelioid hemangioendothelioma, and the nodal metastases were high-grade spindle cell and epithelioid angiosarcoma with necrotic areas and many mitotic figures. This case was seen also by Dr. Rosai (who concurred with the final diagnoses) and is partly illustrated in the Series of articles on soft tissue tumor currently appearing in the journal *Pathologica* (Bisceglia M, Fisher C, Suster S, Kazakov DV, Cooper K, Michal M. *Tumoral, quasitumoral and pseudotumoral lesions of the superficial and somatic soft tissue: new entities and new variants of old entities recorded during the last 25 years. Part VI: Excerpta IV. IV-1: Acquired elastotic hemangioma. IV-2: Epithelioid hemangioendothelioma of soft tissue and skin. IV-3: Extraneuraxial hemangioblastoma of soft tissue and skin. IV-4: Tumor of Dabska arising on lymphangioma*. *Pathologica* 2005;97:10-22). Other questions relating to your case: were there any skin/soft tissue lesions? Bone lesions?

**Ira Bleiweiss:** Agree. Wow!

**John Chan:** This case does not show the typical growth pattern of epithelioid hemangioendothelioma in the liver – and the chondromyxoid stroma and cytoplasmic vacuolation are also lacking. There is too much vascular formation for an epithelioid hemangioendothelioma. I favor a diagnosis of disseminated angiosarcoma.

**Tom Colby:** Agree with diagnosis. This is a unique histology for me. I would probably put this more into the epithelioid angiosarcoma camp, but sometimes the distinction between epithelioid angiosarcoma and hemangioendothelioma with significant atypia is somewhat arbitrary (and determined only by the gods of soft tissue pathology).

**Kum Cooper:** Interesting that there is such a prominent intra-vascular growth pattern. To me this looks like epithelioid angiosarcoma (rhabdoid features with large nuclei and prominent nucleoli). Look forward to hearing what the STT gurus think!

**Ivan Damjanov:** Agree

**Otto Dietze:** Unusual type of hepatic involvement, but I agree with the diagnosis.

**Hugo Dominguez-Malagon:** Should we call this case "intravascular angiosarcomatosis"?

**Goran ElMBERGER:** This is always a very difficult diagnosis. I agree with manifestation of an epithelioid vascular tumor of intermediate (?) malignancy based on cell morphology i.e.: epithelioid cells, excentric nuclei, vasoformative cytoplasmic vacuolization. The overwhelming intravascular distribution in the liver as well as the information on pulmonary metastases makes it difficult – as is often the case – to assign a primary site. In the literature one often reads of multicentric presentation but this may well be a sign of early intravascular permeation and early metastases. Last case I saw had a much longer history with multicentric distribution including liver at presentation 15 years before the patient finally succumbed. In the interval she also suffered from colonic and ovarian carcinoma as well as a classical chondrosarcoma in a rib. I believe she died from EH.

**Vincenzo Eusebi:** Incredible intravascular angiosarcoma. Were other organs involved in addition to the liver and lung?

**Giovanni Falconieri:** Tough case. Never seen something like this outside textbooks. The strikingly permeative growth pattern by the neoplastic cells makes the spectrum of differential diagnosis quite broad. With the purported antigenic profile I can't offer a better microscopic interpretation

**Cyril Fisher:** EHE seems a good diagnosis notwithstanding the absence of CD34.

**Christopher Fletcher:** Given the described immunophenotype, then indeed this seems to represent disseminated epithelioid hemangioendothelioma (or perhaps epithelioid angiosarcoma given the degree of pleomorphism) – it seems that epithelioid endothelial neoplasms such as this certainly show remarkable vasculocentricity in some patients, although the extent of intravascular spread in this particular case seems quite remarkable.

**Jeronimo Forteza-Vila** In the hepatic parenchymal, there are centrolobular vein necrosis, in connection with suprahepatic vein obstruction. It causes problems with the differential diagnosis with metastatic melanoma. I agree with the diagnosis.

**Masaharu Fukunaga:** A very interesting case! Intravascular spread is very prominent. Although its pattern is glomeruloid, it seems to be Dabska's tumor. Thank you very much for sharing the wonderful case.

**Thomas Krausz:** On the slide I received it looks more like epithelioid angiosarcoma with intravascular spread. Striking "rhabdoid" phenotype of the tumor cells. If I did not know the CD31 positivity I would have a broad differential, including metastatic melanoma.

**Janez Lamovec:** While most of the tumor cells appear to be in preexistent vessels, at least some of the vascular spaces are lined by tumor cells. Cells are definitively epithelioid, some with intracytoplasmic lumina but overall appearance of the lesion is so different from what is the usual presentation of epithelioid hemangioendothelioma that I really wonder whether epithelioid angiosarcoma wouldn't be a better term.

**Thomas Mentzel:** Given the predominant intravascular growth of atypical epithelioid (sometimes even plasmacytoid) cells and the absence of stromal changes seen in typical cases of epithelioid hemangioendothelioma it represents a very difficult case for me.

**Markku Miettinen:** Agree on a hemangioendothelioma-like process with apparently purely intravascular proliferation, does not seem typical of epithelioid hemangioendothelioma. Considering prominent intravascular distribution, would hope that thorough search of possible peripheral soft tissue primary was undertaken to rule out the possibility that the liver tumor is a metastasis.

**Elizabeth Montgomery:** This is fascinating. The cells look more pleomorphic than those of epithelioid hemangioendothelioma [EHE] and more like those of epithelioid angiosarcoma. In some of the vessels, the process appears to have come from another area since there appear to be normal endothelial cells but in other places, the lining of the vascular spaces appears neoplastic [which is more like EHE]. This is most unusual.

**Juan Rosai:** I agree with the diagnosis of an *epithelioid malignant vascular neoplasm* for this interesting lesion involving the liver, but I wonder whether the degree of atypia is such as to justify a diagnosis of epithelioid angiosarcoma rather than epithelioid hemangioendothelioma.

**Dominic Spagnolo:** I have to say looking at the slide blind I thought this was going to be a carcinoma with intravascular embolization. Have not encountered this with a hemangioendothelioma. Are the bile duct changes secondary to obstruction? Von Myenburg complexes?

**James Strauchen:** Intravascular epithelioid hemangioendothelioma ("hepatic IVBAT") versus epithelioid angiosarcoma. I am not sure just how "low-grade" this actually is!

**Lawrence Weiss:** I certainly have not seen anything like this before. Angiosarcoma might be appropriate at this point with the atypica seen.

**Bruce Wenig:** The vessels are stuffed with epithelioid neoplastic cells that have a plasmacytoid appearance, at least to me. I considered a plasmacytic hemolymphoid neoplasm or an epithelial neoplasm with plasmacytoid cell features, but honestly I did not consider the possibility of an endothelial neoplasm as I did not appreciate features suggesting endothelial cell origin. Great case.

#### **CASE NO. 15— CONTRIBUTED BY: DR. SICKEL**

**Phil Allen:** Seminoma associated with hyperplasia and cystic dilatation of the rete testis, left orchidectomy. I was not aware of the condition and would probably have wrongly interpreted the spaces lined by cuboidal cells as dilated vessels.

**Carlos Bacchi:** Great case and beautiful gross picture.

**David Ben-Dor:** There are some moderately dilated ductal like structures on the slide but I didn't see anything looking like the colloid cysts documented on the photo- was I supposed to. The seminoma cells themselves look to me a little smaller and monomorphic than what I'm accustomed to seeing in this tumor- are spermatocytic features kicking in here? Very little inflammation. The extensive

hemorrhagic necrosis is surprising- torsion? Pressure from the abnormal cysts? I respect your circumspection in dealing with the oncologist over the issue of thyroid differentiation- an interesting observation but with possible dangerous ramifications if not handled sensitively.

**Gerald Berry:** My first thought was mixed seminoma and teratoma but then I looked more closely at the glandular component. Nice case.

**Michele Bisceglia:** Seminoma with associated hyperplasia and cystic dilatation of rete testis. Nice case. Speaking of the "dilatation of rete testis" it comes to mind the fact that there's also another (different) condition in which dilatation may occur - rete testis dysplasia. This latter condition usually affects infants, being a congenital condition usually associated with unilateral extreme form of renal hypoplasia (Wojcik LJ, Hansen K, Diamond DA, Koyle M, Koff SA, Coplen DE, Caldamone AA. Cystic dysplasia of the rete testis: a benign congenital lesion associated with ipsilateral urological anomalies. J Urol 1997;158:600-4.). Rete testis cystic dysplasia is due to incorrect conjunction of rete testis tubules (which are of sex-cord stromal tissue derivation) and the efferent ductules of the epididymis which are of mesonephric derivation. Pictures of cystic dysplasia of rete testis are illustrated in AFIP vol. 25 (3<sup>rd</sup> series) at pag. 326, and in a recent paper published in Adv Anat Pathol (Bisceglia M, et al. Renal cystic disease –a Review. 2006; 13:26-56: Fig. 15A-B).

**Ira Bleiweiss:** Very unusual. This looks just like thyroid.

**Tom Colby:** Agree with diagnosis. A new lesion for me. I think I would have liked the name "struma testicularum" better.

**Kum Cooper:** At first I thought that this was a seminoma with tubules (as described in the recent literature). Hyperplasia of the rete testis has also been described in undescended testis. I wonder if this patient's testis was undescended (previously or present!). (Adenomatous Hyperplasia of the Rete Testis in the Undescended Testis. J Path 1990, 162; 333-334).

**Ivan Damjanov:** Agree.

**Otto Dietze:** I did not see this before, thank you.

**Hugo Dominguez-Malagon:** I was fooled by the cystic struma-like component, thank you.

**Goran Elmberger:** Very interesting observation. I wonder if this could be remnants of pre-existing or possibly predisposing pathology. Tubuli look very atrophic. There is a rare congenital condition named cystic dysplasia that shares some of these features. Bilateral findings? Ultrasound? Definitely makes it difficult to stage with respect to rete involvement. IHC double staining??

**Vincenzo Eusebi:** Cystic dilatation of rete testis and seminoma.

**Giovanni Falconieri:** Nice case, thanks Josh. I have never seen similar cases.

**Cyril Fisher:** Cystic dilatation of rete testis with seminoma, striking appearance. Does this count as rete involvement for management purposes?

**Christopher Fletcher:** This lesion does indeed seem to show remarkable cystic dilation of the rete testis, certainly beyond anything which I have personally seen before – I can well understand why this could easily be confused with a separate neoplastic component.

**Jeronimo Forteza-Vila:** Thank you for this interesting case.

**Masaharu Fukunaga:** It seemed to be a mixed germ cell tumor, seminoma and teratoma (thyroid tissue). A very a beautiful and educational case. Thank you very much for the slide and description.

**Thomas Krausz:** I also favor cystic dilatation of the rete testis secondary to compression/obstruction by the adjacent seminoma. The colloid-like secretion is impressive.

**Janez Lamovec:** Most interesting case. One would really think of thyroid follicles but a negativity for thyroglobulin in so well differentiated "thyroid" epithelium would be most improbable. Never seen before. Thank you.

**Thomas Mentzel:** Many thanks for sharing these unusual findings in a case of seminoma.

**Markku Miettinen:** Fully agree on seminoma, with a cystic rete testis proliferation.

**Juan Rosai:** Nice classical seminoma associated with cystic dilatation of the rete-testis. Of course, it is important no to confuse the latter with a non-seminomatous component of the germ cell tumor.

**Dominic Spagnolo:** I agree with seminoma and rete testis hyperplasia. Have seen this a few times before. The very first time was in 1983/4, where I saw an extremely florid case, together with hyaline globules all over the place, that we thought (erroneously) that we were dealing with a yolk sac tumor component. This is a very nice example - thank you.

**James Strauchen:** Seminoma with hyperplasia of the rete testis. The rete hyperplasia is striking and could be easily confused with yolk sac tumor or thyroid colloid ("struma testis"). Thank you for this informative case!

**Lawrence Weiss:** I've seen the phenomenon before, but not to the extent seen in this case.

**Bruce Wenig:** I also haven't seen a seminoma with associated hyperplasia and cystic dilatation of the rete testis. Nice case.

#### **CASE NO. 16 — CONTRIBUTED BY: DR. SPAGNOLO**

**Phil Allen:** Benign microglandular proliferation, right nasal mucosa. I don't think I have seen anything like this before but I think it is benign. It could well be the same as the condition described by Chuan and Lin.

**Carlos Bacchi:** I believe the lesion is benign. I would call it polypoid complex adenosis.

**David Ben-Dor:** There is definitely a striking proliferation with many small glands but some larger ones strewn in a somewhat haphazard fashion, reminding me in a way of syringoma. Why can't this be REAH? This entity can show a combination of glands of varying sizes, with the small glands predominating in this particular instance. In any case I think that despite the infiltrative appearance this is benign (though to be truthful if it were my case I would probably show it to someone to be on the safe side). Bruce wrote the classical paper on this entity- it would be interesting to read his comments.

**Gerald Berry:** I would be interested in Dr. Wenig's opinion on this one. It seems like the degree of proliferation is more than you would expect for a respiratory epithelial adenomatoid hamartoma. The eosinophilic luminal secretions of microglandular adenosis are absent. Perhaps adenosis, not otherwise specified arising in a nasal polyp.

**Michele Bisceglia:** Agree, Dominic. I think it is a benign reactive proliferation.

**Ira Bleiweiss:** I don't know what name to give this, but I think its benign. Time will tell.

**John Chan:** Unusual case I have not seen before. The lack of myoepithelial cells around the proliferated small glands may raise a possibility of low grade adenocarcinoma of the sinonasal tract (the designation "adenocarcinoma" is applied rather liberally in this site), I am also in favor of a benign process, because these tubules (semi-oncocytic) merge so well with the obviously benign glands, the proliferated glands are located predominantly in the superficial zone, and there is no destructive growth. "Microglandular adenosis" may sound good, but may be objectionable because there are many narrow tubules quite unlike the breast counterpart. Or perhaps "microglandular hyperplasia", but then it really does not look like the cervical counterpart.

**Tom Colby:** Tough case. I went back and forth several times and finally settled on nonneoplastic because there were some regions where the small glands appeared to have somewhat of a lobular character and because there are regions where there was also a peculiar stromal proliferation that appeared independent of the small glands.

**Kum Cooper:** Dom, another fascinoma from down under!! Going down south it reminded me of adenomatoid tumor or nephrogenic adenoma (or metaplasia). I agree this does not look like REAH; but I have no better suggestion than MGA (are they EMA negative?). A focus on one of the polyps looked like sino-nasal HPC!

**Ivan Damjanov:** I did not think that this lesion deserves any fancy name. Benign , reactive.

**Otto Dietze:** I suggest a benign lesion, consistent with microglandular adenosis.

**Hugo Dominguez-Malagon:** I would consider the possibility of a polymorphous low-grade adenocarcinoma of accessory glands.

**Goran Elmberger:** Challenging case. My first inclination was to diagnose lesion as a low-grade adenoca then I started thinking of SNITACS with Paneth cell metaplasia. In the end I am very uncertain. One intriguing feature is the stroma that to me looks almost of ovarian type. Microglandular atypical proliferation – low-grade cancer can not be excluded. Certainly look forward to other comments.

**Vincenzo Eusebi:** I did object to the case reported in Histopathology (36:373-384, 2000) that it was not histologically similar to microglandular adenosis of the breast. I also objected that six month FU was a too short period to exclude malignancy. I have seen 2 of such cases since then, and the present one is the 3<sup>rd</sup>. I still think that these lesions are not similar to microglandular adenosis of the breast. In spite of the fact that in the present case there is invasion of nerves, I cannot make up my mind on the nature of these cases. The two cases I have seen did not recur (2 and 3 years FU). Therefore at the moment I think that these lesions are at the most of low-grade malignancy potential.

**Giovanni Falconieri:** May be that I jumped early to conclusions, but microglandular adenosis-like changes are prominent and this is the first thing that came to my mind. I also believe this is benign.

**Cyril Fisher:** Given its single cell layer, infiltrative nature, perineurial involvement and the location it would seem appropriate to follow it up as for a low grade carcinoma. The case in Histopathology had no recurrence in 16 months but that is not very long. Great case, Dom.

**Christopher Fletcher:** I have never personally seen anything like this at this anatomic site – however, your use of the term “adenosis” certainly seems very reasonable, particularly in the setting of an intact myoepithelial layer. Some of the adjacent stromal tissue also appears to be abnormal, with notable hypercellularity – I wonder if these findings are in any way associated with one another. I will be interested to hear the comments of the head and neck experts in our panel.

**Jerónimo Forteza-Vila:** I agree with the possibility of microglandular adenosis.

**Masaharu Fukunaga:** It is an interesting case, Dominic. I prefer a respiratory epithelial adenomatoid hamartoma with microglandular hyperplasia.

**Thomas Krausz:** I favor benign, some strange type of “microglandular” adenosis.

**Janez Lamovec:** I am not sure how to name this but it appears to me as some kind of adenosis. In foci, it does somewhat resemble microglandular adenosis, elsewhere it is more tubular. Most of these proliferating ductules are surrounding larger dilated ducts giving an organoid appearance to the lesion. I believe that the architectural and cytological aspects of the lesion are in favor of a benign condition.

**Thomas Mentzel:** Despite the striking variations in size and shape of the glandotubular neoplastic structures and the presences of small and diffusely infiltrating glands, I agree with your diagnosis of a benign adenomatosis-like epithelial lesion.

**Markku Miettinen:** Nasal polyp with adenomatous proliferation; seems to stop, does not look malignant.

**Elizabeth Montgomery:** Looks like some sort of adenosis to me but this claim made with no scholarly backing.

**Santiago Ramon y Cajal:** Agree that the lesion looks benign. I am favor to microglandular adenosis

**Juan Rosai:** I found this the most difficult case of the whole set. As indicated in the discussion, the differential diagnosis is between an extremely well-differentiated tubular type carcinoma and a benign lesion with a microglandular adenosis pattern. I slightly favor the diagnosis of tubular-type adenocarcinoma because of the very complex architecture, but I am not 100% sure. What bothers me is that about a month ago I saw a similar case in consultation which I called benign. Maybe I should look at it again.

**James Strauchen:** I have never seen anything like this and considered a variant of low-grade polymorphous adenocarcinoma of minor salivary type.

**Saul Suster:** My first thought was an adenomatoid tumor. Don't have a name for this but I favor a benign process. Will defer to Bruce Wenig' opinion.

**Lawrence Weiss:** Who knows what this is, but it is benign. Could the stromal proliferation between primary and the epithelial proliferation secondary. Did the S-100 stain a lot of the funny stromal cells?

**Bruce Wenig:** Well, having seen a few sinonasal lesions I can honestly say this is one that I have not exactly seen before. It is not a respiratory epithelial adenomatoid hamartoma or at least not one that I have previously seen. My initial consideration was that of a benign lesion, possible hamartomatous, but it does not quite fit into a previously defined category. The pattern of growth, presence of single cells lining the small tubules, focal back-to-back growth and absence by p63 staining of myoepithelial cells are all disconcerting findings. Focally, tubules are present around small nerves, the latter apparently highlighted by the S100 protein staining. I am inclined to consider this lesion as a sinonasal low-grade adenocarcinoma, non-salivary gland, non-intestinal type, with the recommendation for conservative but complete excision of any remaining lesion. There is a separate area in my slide of an unencapsulated submucosal benign spindle cell proliferation with neurogenic features; was this focus diffusely S100 protein positive? It may represent a coincidental small benign peripheral nerve sheath tumor (benign Schwannoma). Tough case; I look forward to reading what everyone else thought of this lesion.

#### **CASE NO. 17 — CONTRIBUTED BY: DR. WENIG**

**Phil Allen:** Undiagnosed, histologically bland, focally myxoid, weakly EMA positive tumor with prominent vessels and perivascular hyalinization, right sphenoid region, basal of skull and right nasal cavity. Despite the positive EMA stain, I agree that it is not very convincing for a meningioma and I have to confess to being a profound disbeliever in the existence of glomangiomyopericytoma, possibly because I am not as Stout as I once was. I have even lost my faith in hemangiopericytoma. What must I do to be saved?

**Carlos Bacchi:** I believe this is suspicious for meningioma.

**David Ben-Dor:** The cells at first glance look gemistocytic, bringing to mind a low grade astrocytoma (as long as you're talking about a possible CNS lesion) but by current standards of practice this would be untenable given the GFAP negativity. I assume one of the unnamed consultants was an experienced neuropathologist.

**Michele Bisceglia:** I do not think this is a meningioma (atypical variant). I concur with the possibility of a tumor you propose in the spectrum of glomangiopericytoma/HPC (sinonasal type). Any choice for EM analysis from paraffin embedded material?

**Ira Bleiweiss:** I like atypical meningioma.

**John Chan:** I favor a diagnosis of meningioma. The EMA positivity also goes along with it. In some variants of meningioma (such as the microcystic variant), there can be a striking vascularity.

**Kum Cooper:** Bruce, morphologically I thought that this represented a meningioma and the IHC is supportive. Have you tried EM...that may be helpful!

**Otto Dietze:** Sinonasal HPC seems to me the best diagnosis.

**Hugo Dominguez-Malagon:** Meningeal hemangiopericytoma (or angioblastic meningioma), in a previous AMR seminar I presented a case that by histology and immunohistochemistry was HPC, however by electron microscopy it contained typical meningeal processes, again the exact histogenesis of these neoplasms is not well settled.

**Goran Elmberger:** Hello Bruce. Difficult case. I do not have any better dx than those suggested by yourself. Could it be angiomatoid variant of meningioma. Ganglioneuronal differentiation excluded? Not in favor of meningeal hemangiopericytoma. PgR, Synaptophysin and NeuN? Also thought of odd variant of chordoma or recently described sustentacular cell tumor but both these dx should be S100+.

**Vincenzo Eusebi:** I would be happy with the diagnosis of atypical meningioma.

**Giovanni Falconieri:** I would also favor meningioma, locally invasive. I do not know whether to use the appellation of atypical since I could not see necrosis or atypical mitoses, as you rightly pointed out. In our neurosurgeon's experience meningioma may occasionally bleed profusely and sometimes such oozing may create problems when located within darn places such as the spinal canal or the skull base. I agree that because of the location and bone infiltration this lesion may pose critical challenges in patient management. I do not know the alternative entity you mentioned.

**Cyril Fisher:** Some of the cells have long processes - ??perineurioma. EM might be contributory.

**Christopher Fletcher:** This is a tough case, at least without doing one's own immunostains. If the EMA stain is convincingly positive, then, personally, I think that the morphology would fit better with an unusual meningothelial lesion, rather than a tumor in the myopericytic spectrum. I cannot convince myself that the tumor cells are really arranged in a convincingly perivascular pattern. Instead, this seems to be a more diffuse sheet-like proliferation of pale staining cells with rather ovoid nuclei. It's hard to come up with a definitive diagnosis...

**Jeronimo Forteza-Vila:** I don't know if there was a previous surgical intervention, so it would be a Gauzoma. It would be a reactive meningiomatosis in connection with the surgical material employed.

**Masaharu Fukunaga:** My impression is clear cell meningioma. It is a very difficult case. Thank you very much.

**Thomas Krausz:** I favor a variant of meningioma.

**Janez Lamovec:** I would favor some myopericytic lesion in this case. The slide is relatively pale, probably also due to edema and the vessels that are numerous don't have, for the most part, a typical staghorn appearance. The cells appear myoid focally, and their perivascular arrangement is also focally suggested. However, the morphology of this tumor is not that of a more typical example of myopericytic neoplasm. In regard to the biological potential of this lesion, I think it would be the best to put it into the "uncertain" category.

**Thomas Mentzel:** For me the morphological features are more consistent with an atypical meningioma in my opinion, since sinonasal hemangiopericytoma represents a myogenic neoplasm with a hemangiopericytoma-like vascular pattern.

**Michal Michal:** Meningioma with atypical cells.

**Markku Miettinen:** Meningioma variant would be my favorite; may not fulfill strict definition for atypical meningioma. CK18 might be of interest (often positive in different types of meningiomas). Has similar "angiomatoid" appearance as seen in some CNS meningiomas.

**Elizabeth Montgomery:** Looks like a peculiar meningioma to me.

**Santiago Ramon y Cajal:** Difficult case. First, I favored a vascular tumor, within the category of a glomangiomyopericytoma. I understand that the tumor shows positivity to muscle specific actin.



**Juan Rosai:** My differential diagnosis is also between an atypical meningioma and a tumor in the glomangiopericytoma family. I favor meningioma because of the EMA positivity, the scattered hyperchromatic large nuclei, and the nuclear pseudoinclusions.

**Dominic Spagnolo:** I agree more with your thinking than meningioma - I don't like it at all for meningioma. It looks like an "angiofibromatous" tumor of some description, would not argue against your notion of it being related to glomangiomyopericytoma. It struck me as having some features seen both in pleomorphic hyalinizing angiectatic tumor, and extra-orbital giant cell angiofibroma, though not typical of either. I don't have a specific diagnosis. Would be cautious in predicting behavior as it seems clinically to be locally aggressive.

**James Strauchen:** Clear-to-eosinophilic cells and striking vascularity. ? sinonasal HPC ? PEComa

**Saul Suster:** My vote goes for meningioma.

**Lawrence Weiss:** I don't know about anyone else, but I am completely demoralized about learning yet again that there is so much I have no clue about.