JAN 2021 DIAGNOSIS LIST

21-0101: glomus tumor (lung; lung pathology)

21-0102: invasive non-keratinizing squamous cell carcinoma with DEK-AFF2 fusion (nasopharynx, H&N pathology)

21-0103: anastomosing hemangioma (liver; liver pathology)

21-0104: gastrointestinal neuroectodermal tumor (soft tissue; soft tissue & GI path)

21-0105: metastatic YWHAE-NUTM2A rearranged high grade endometrial stromal sarcoma (mediastinum/GYN pathology)

21-0106: metastatic prostate cancer and lymphoplasmacytic lymphoma (bone marrow; hematopathology)

21-0107: Sertoli cell nodules with GCNIS (testis; GU pathology)

21-0101

Greg Rumore; Kaiser Diablo

62-year-old M with 2cm subpleural nodule right lung base.









Differential Diagnosis

- Glomus tumor
- Neuroendocrine tumor (carcinoid)







IHC

- Pancytokeratin-negative
- EMA-negative
- SMA-positive
- MSA-positive
- Synaptophysin-focally positive
- Chromogranin-negative
- TTF-1-negative
- Sox-10-negative

Glomus Tumor

- Glomus tumor-mesenchymal neoplasm composed of cells resembling the modified smooth muscle cells of normal glomus body
- Vast majority in distal extremities, but can occur anywhere
- Small uniform, round cells with central nucleus, well defined cell borders

Glomus Tumors of Lung

- Male predominance
- Average age-48
- Symptoms-hemoptysis, dyspnea, pneumothorax, postobstructive sx.
- Average size=2.2 cm.
- Endobronchial (polypoid) or peripheral (circumscribed)
- Sheets and clusters of glomus cells frequently arranged around small vessels
- Nuclei small and round, diffuse fine chromatin

Malignant Glomus Tumor

- Marked nuclear atypia and mitotic activity or any atypical mitoses
- Infiltrative growth, necrosis, or hemorrhage
- At least one atypical histologic feature, but not meeting criteria for malignancy=uncertain malignant potential (UMP)
- 2013 WHO- deep or visceral location and size > 2cm=UMP

21-0102

Armen Khararjian; Kaiser Walnut Creek

59-year-old F right nasopharyngeal mass.

































Non-Keratinizing Squamous Cell CA of Sinonasal Tract

- Most tumors of this site are either viral induced or rarely have specific molecular alterations
 - EBV, HPV, BRD4-NUT, ESWR1-FLI
 - Some don't though...

Non-Keratinizing Squamous Cell CA of Sinonasal Tract with DEK-AFF2 Fusion

- Immature, transitional type epithelium growing as papillary structures with deep, broad stromal ribbons
- Cytology
 - Monotonous, round to oval nuclei
 - Vesicular chromatin
 - Amphophilic cytoplasm
 - Vague nuclear palisading
- Other features
 - Increased mitoses, focal tumor necrosis, neutrophilic infiltrate, involve middle ear

IHC and Molecular

- Positive for squamous markers
 - CK5, p40, p63
- EBV negative
- p16 negative
- DEK-AFF2 fusion with breakpoints of DEK exon 7 and AFF2 exon 6

Reported Cases Thus Far

Case No.	Age/Sex	Location	Clinical Course	References
1	Not reported	Skull base	Unresectable with lung metastases, dramatic response to PD-L1 inhibitor	Yang et al ⁴
2	Late 60s/male	Middle ear, temporal bone, nasopharynx, nasal cavity	Surgical debulking, under evaluation for systemic management	Todorovic et al
3	Late 40s/male	Middle ear, temporal bone	Unresectable with regional neck metastases and lung metastases, treated with radiotherapy	Todorovic et al
4	28/female	Nasal cavity, orbit	Surgical debulking, induction chemotherapy with cisplatin/5FU, with excellent response. Definitive treatment pending completion of pregnancy	This study

Non-Keratinizing Squamous Cell CA of Sinonasal Tract with DEK-AFF2 Fusion

- Distinctive head and neck tumor?
 - Further refinement of "poorly differentiated sinonasal carcinoma"
References

- Todorovic E, et al. Middle ear and temporal bone nonkeratinizing squamous cell carcinomas with DEK-AFF2 fusion: an emerging entity. Am J Surg Pathol. 2020;44: 1244–1250
- Bishop, Justin A, et al. Nonkeratinizing Squamous Cell Carcinoma of the Sinonasal Tract With *DEK-AFF2* Further Solidifying an Emerging Entity. Letter to Editor. AJSP Sept 29, 2020.

21-0103

Sanjay Kakar; UCSF

51-year-old F with NASH cirrhosis. Liver mass on imaging which grew from 1.1cm to 1.6cm over 2 years. Enhancement pattern not typical of hemangioma on imaging and suspicion of HCC was raised.

History

- 51/F with NASH cirrhosis
- Liver mass on imaging which grew from 1.1 cm to 1.6 cm over 2 years
- Enhancement pattern not typical of hemangioma on imaging and suspicion of HCC was raised















Pancytokeratin







CD3











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SB meeting: Case 21-0103

Diagnostic considerations

Cirrhosis: HCC, cholangiocarcinoma





Pancytokeratin















CD68



Diagnostic considerations

- Cirrhosis: HCC, cholangiocarcinoma
- Hematopoietic neoplasm
- Other keratin-negative tumors

Adrenocortical carcinoma Paraganglioma GIST (KIT-negative) Melanoma

Angiomyolipoma

S-100









ERG





Vascular neoplasms

- Hemangioma
- Angiosarcoma
- Kaposi (HHV8-negative)
- Epithelioid hemangioendothelioma







Hepatic small vessel neoplasm Anastomosing hemangioma

Hum Pathol. 2016 Aug;54:143-51. doi: 10.1016/j.humpath.2016.03.018. Epub 2016 Apr 14.

Hepatic small vessel neoplasm, a rare infiltrative vascular neoplasm of uncertain malignant potential.

Gill RM¹, Buelow B², Mather C², Joseph NM², Alves V³, Brunt EM⁴, Liu TC⁴, Makhlouf H⁵, Marginean C⁶, Nalbantoglu I⁴, Sempoux C⁷, Snover DC⁸, Thung SN⁹, Yeh MM¹⁰, Ferrell LD².

Am J Surg Pathol. 2013 Nov;37(11):1761-5. doi: 10.1097/PAS.0b013e3182967e6c.

Anastomosing hemangioma of the liver and gastrointestinal tract: an unusual variant histologically mimicking angiosarcoma.

Lin J¹, Bigge J, Ulbright TM, Montgomery E.





HSVN: hobnailing, minimal atypia



Thin walled vessels, infiltrating architecture



Ki-67 low, p53 not diffuse



HSVN/Anastomosing hemangioma

- Mild cytologic atypia, no mitoses
- EMH, hyaline globules, thrombosis
- AH associated with cavernous hemangioma (not HSVN)
- HSVN reported in cirrhosis (not AH)
- HSVN-infiltrative, AH- circumscribed
- Unusual features (current case)

Compressed vasculature Abundant histiocytes
HSVN/Anastomosing hemangioma

- No reported recurrence/metastasis
- GNAQ, GNA14, GNA11 mutations
- Resemblance to vascular skin tumors:
 - Sinusoidal hemangioma
 - Hobnail hemangioma
 - Retiform hemangioendothelioma

Diagnosis: Anastomosing hemangioma

Well-circumscribed

21-0104

Sarah Zadeh/Brooke Howitt; Stanford

53-year-old F presents shortness of breath and a large mediastinal mass. No known prior history of malignancy. FNA of mediastinal mass performed.













Diagnosis?

Malignant Epithelioid Neoplasm (See Comment.)

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Original Article

YWHAE-NUTM2A/B Translocated High-grade Endometrial Stromal Sarcoma Commonly Expresses CD56 and CD99

W. Glenn McCluggage, F.R.C.Path. and Cheng-Han Lee, M.D.

Me:

Please send patient's prior hysterectomy for our review at Stanford!

Clinical Team:

But it was benign...what is there to review?





YWHAE FISH











YWHAE-NUTM2A

International Journal of Groucological Pathology 201525-532, Lippincott Williams & Wilkins, Baltimote Copyright © 2018 by the International Society of Gynecological Pathologists

Original Article

YWHAE-NUTM2A/B Translocated High-grade Endometrial Stromal Sarcoma Commonly Expresses CD56 and CD99

W. Glenn McCluggage, F.R.C.Path. and Cheng-Han Lee, M.D.

YWHAE-NUTM2A/B Translocated HGESS

- Variant of HGESS which is clinically aggressive and diffusely coexpresses CD99 and CD56
- Not uncommon for these tumors to present with extrauterine disease
- Associated with a component of LGESS with a fibromyxoid stroma (CD10-; Cyclin D1/CD117/BCOR+)
- Invokes a DDx that includes SRBCTs: Ewing sarcoma (CD99+), neuroendocrine carcinoma (CD56+), malignant GIST (CD117)
- Uterine tumor resembling ovarian sex cord tumor (UTROSC) is another uterine mesenchymal neoplasm which is commonly CD56/CD99+

21-0105

Dave Bingham; Stanford

42-year-old M with abdominal mass.





























Additional immunostains

• Negative for MiTF, melan A, HMB45, synaptophysin, INSM1, DOG1, PRAME
Clear Cell Sarcoma-like Tumor of the GI tract (Malignant Gastrointestinal Neuroectodermal Tumor)

Histomorphology

- Sheets and nests of epithelioid to oval to spindled cells with eosinophilic to clear cytoplasm, small nucleoli, uniform vesicular nuclei and scattered mitotic figures
- Frequently contain multinucleated osteoclastlike giant cells (not seen in current case)

Immunohistochemistry

- Positive for S100 and SOX10
- Negative for c-kit, desmin, ckmix
- Negative for HMB-45, melan A, MiTF

Electron Microscopy

- Dense-core secretory granules and clear secretory vesicles
- Slender or bulbous cytoplasmic processes often with synapse-like structures
- Negative for melanocytic differentiation

Molecular Genetic Findings

 Most show Ewing sarcoma breakpoint region 1 gene (EWSR1) translocations (chromosome 22)

• Partner fusion genes include ATF1 and CREB1

• FISH shows split signal consistent with chromosomal translocation involving EWSR1

Discussion

Clear cell sarcoma of the tendons and aponeuroses (CCSTA) is similar to yet different from melanoma

-Similar in that it is usually positive for melanoma markers (malignant melanoma of soft parts)

-Different in that it usually has EWSR1 translocations but melanoma does not

Clear cell sarcoma-LIKE tumor of the GI tract is usually negative for melanoma markers HMB-45, Melan A, MiTF

Clear cell sarcoma-LIKE tumor of the GI tract is similar to CCSTA in that both usually have EWSR1 translocations

So these tumor are all cousins

- All derived from primitive neural crest cells
- All S100, SOX10 positive

Clinical features

• Very rare tumor

• Affects sexes equally, can affect children and adults with mean age of 42 years

• Poor prognosis. Most patients die of disease

Differential Diagnosis

- GI Stromal Tumor ---DOG1 and ckit +
- Melanoma and True Clear Cell Sarcoma (CCSTA) involving GI tract --- melanoma specific markers +
- Carcinoma ---CK+
- Leiomyosarcoma ---desmin +
- Malignant peripheral neurve sheath tumor –H3K27me3-
- Monophasic synovial sarcoma ---CK +, SYT rearrangement
- Neuroendocrine tumor --syn+
- IPOX and FISH for EWSR1 can solidify diagnosis

Reference

 Stockman DL, et al. Malignant Gastrointestinal Neuroectodermal Tumor: Clinicopathologic, Immunohistochemical, Ultrastructural, and Molecular Analysis of 16 Cases With a Reappraisal of Clear Cell Sarcoma-like Tumors of the Gastrointestinal Tract. Am J Surg Pathol. 2012



Dean Fong; VA Palo Alto

70-year-old Veteran with h/o prostate cancer and Agent Orange exposure, was admitted after routine bloodwork demonstrated a hemoglobin level of 5.1 g/dL, and platelet count of 116x109/L. A complete metabolic panel showed elevated alkaline phosphatase and total protein (8.2 g/dL). Serum immunofixation demonstrated an abnormal lambda monoclonal IgM band (Mprotein 1.94 g/dL) with an elevated lambda-to-kappa ratio.









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Pancytokerati n



NKX3.1



CD20

In-situ Hybridization

Карра



Lambda



Flow Cytometry

- ATYPICAL LAMBDA MONOTYPIC B CELL POPULATION, 40%, EXPRESSING CD19, CD20, AND PARTIAL CD38
- NOT EXPRESSING CD5 OR CD10

Diagnosis

- Metastatic Prostatic Adenocarcinoma
- Lymphomplasmacytic Lymphoma
 - MYD88 Detected

Agent Orange

- Agent Orange refers specifically to a 50:50 formulation of 2,4-D and 2,4,5-T
- Stored in barrels identified by an orange band
- Term has come to often be used more generically to refer to all the herbicides sprayed by the U.S. military in Vietnam
- Tactical herbicide used by the U.S. military for control of vegetation between 1962-1971
- Lack of accurate estimate of chemical exposure
- Wikipedia \rightarrow 4 million



A U.S. Huey helicopter sprays Agent Orange over Vietnam. The U.S. military used at least 11 million gallons of Agent Orange in Vietnam from 1961 to 1972. Wikimedia Commons

Agent Orange

- The two active ingredients in the Agent Orange herbicide combination were equal amounts
 - 2,4-dichlorophenoxyacetic acid (2,4-D), and
 - 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)
 - Contained traces of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).
- The dioxin TCDD was an unwanted byproduct of herbicide production.
- Dioxins are pollutants that are released into the environment by burning waste, diesel exhaust, chemical manufacturing, and other processes.
- TCDD is the most toxic of the dioxins and is classified as a human carcinogen by the Environmental Protection Agency.

Dioxin TCDD

- Adverse health effects of dioxin exposure in humans may include:
 - Cardiovascular disease
 - Diabetes
 - Cancer
 - Porphyria
 - Endometriosis
 - Early menopause
 - Reduced testosterone and thyroid hormones
 - Altered immunologic response
 - Skin, tooth, and nail abnormalities
 - Altered growth factor signaling
 - Altered metabolism

H.R.556 - Agent Orange Act of 1991 102nd Congress (1991-1992)

- Directs the Secretary of Veterans Affairs to regulate and determine service connection of Veterans exposed to Agent Orange
- Directs the Secretary to enter into an agreement with the National Academy of Sciences (NAS) under which NAS shall review and summarize the scientific evidence (and its strength) concerning the association between exposure to a herbicide agent during service in Vietnam and each disease suspected to be associated with such exposure
- Extends benefits

Between January 9, 1962, and May 7, 1975, you must have served for any length of time in at least one of these locations:

- In the Republic of Vietnam, or
- Aboard a U.S. military vessel that operated in the inland waterways of Vietnam, or
- On a vessel operating not more than 12 nautical miles seaward from the demarcation line of the waters of Vietnam and Cambodia, or
- On regular perimeter duty on the fenced-in perimeters of a U.S. Army installation in Thailand or a Royal Thai Air Force base. These bases include U-Tapao, Ubon, Nakhon Phanom, Udorn, Takhli, Korat, or Don Muang.

Or at least one of these must be true. You:

- Served in or near the Korean DMZ for any length of time between September 1, 1967, and August 31, 1971, or
- Served on active duty in a regular Air Force unit location where a C-123 aircraft with traces of Agent Orange was assigned, and had repeated contact with this aircraft due to your flight, ground, or medical duties, or
- Were involved in transporting, testing, storing, or other uses of Agent Orange during your military service, or
- Were assigned as a Reservist to certain flight, ground, or medical crew duties at one of the below locations.

Eligible Reserve locations, time periods, and units include:

- Lockbourne/Rickenbacker Air Force Base in Ohio, 1969 to 1986 (906th and 907th Tactical Air Groups or 355th and 356th Tactical Airlift Squadrons)
- Westover Air Force Base in Massachusetts, 1972 to 1982 (731st Tactical Air Squadron and 74th Aeromedical Evacuation Squadron, or 901st Organizational Maintenance Squadron)
- Pittsburgh International Airport in Pennsylvania, 1972 to 1982 (758th Airlift Squadron)









TABLE S-1 Summary of the *Eleventh Biennial Update* Findings on Vietnam-Veteran, Occupational, and Environmental Studies Regarding Scientifically Relevant Associations Between Exposure to Herbicides and Specific Health Outcomes

Sufficient Evidence of an Association

Epidemiologic evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between exposure to herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.^b For example, if several small studies that are free of bias and confounding show an association that is consistent in magnitude and direction, there could be sufficient evidence of an association. There is sufficient evidence of an association between exposure to the chemicals of interest and the following health outcomes:

Soft-tissue sarcoma (including heart)

- * Non-Hodgkin lymphoma
- Chronic lymphocytic leukemia (including hairy cell leukemia and other chronic B-cell leukemias)
- * Hodgkin lymphoma

Chloracne

Hypertension (category change from Limited or Suggestive in Update 2014) Monoclonal gammopathy of undetermined significance (MGUS) (newly considered condition)

The committee did not reach consensus on whether the evidence regarding type 2 diabetes (mellitus) was more properly classified as *Sufficient* or *Limited or Suggestive*.



Limited or Suggestive Evidence of an Association

Epidemiologic evidence suggests an association between exposure to herbicides and the outcome, but a firm conclusion is limited because chance, bias, and confounding could not be ruled out with confidence.^b For example, a well-conducted study with strong findings in accord with less compelling results from studies of populations with similar exposures could constitute such evidence. There is limited or suggestive evidence of an association between exposure to the chemicals of interest and the following health outcomes:

- Laryngeal cancer Cancer of the lung, bronchus, or trachea Prostate cancer Cancer of the urinary bladder
- * Multiple myeloma
- * AL amyloidosis Early-onset peripheral neuropathy Parkinson disease (including Parkinsonism and Parkinson-like syndromes) Porphyria cutanea tarda Ischemic heart disease Stroke Hypothyroidism

The committee did not reach consensus on whether the evidence regarding type 2 diabetes (mellitus) was more properly classified as *Sufficient* or *Limited or Suggestive*.



Inadequate or Insufficient Evidence to Determine an Association

The available epidemiologic studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine association between exposure to the chemicals of interest and the following health outcomes that were explicitly reviewed:

Cancers of the oral cavity (including lips and tongue), pharynx (including tonsils), or nasal cavity (including ears and sinuses)	Neonatal or infant death and stillbirth in offspring of exposed people Low birth weight in offspring of exposed people
Cancers of the pleura, mediastinum, and other unspecified sites in the respiratory system and intrathoracic organs	Birth defects in offspring of exposed people, including spina bilda Childhood cancer (including acute myeloid leukemia) or other adverse health outcomes in offspring of exposed people
Esophageal cancer	Neurobehavioral disorders (coonitive and neuropsychiatric)
Stomach cancer	Naurodeoanerative diseases, excluding Parkinson disease
Colorectal cancer (including small intestine and anus)	Chronic perinheral nervous system disorders
Hepatobiliary cancers (liver, gallbladder, and bile ducts)	Hearing Jose
Pancreatic cancer Bone and joint cancers	Respiratory disorders (wheeze or asthma, chronic obstructive pulmonary disease, and farmer's lung)
Melanoma	Gastrointestinal, metabolic, and divestive disorders (changes in heratic enzymes, liver
INOR-melanoma skin cancer (basal-cell and squamous-cell)	disorders including cirrhosis, lipid abnormalities, and ulcers)
Breast cancer	Immune system disorders (immune suppression, afterey, and autoimmunity)
Cancers of reproductive organs (cervix, uterus, ovary, testes, and penis; excluding prostate)	Circulatory disorders (other than hypertension, ischemic heart disease, and stroke)
Renal cancer (kidney and renal petvis)	Endometriosis
Cancers of brain and nervous system (including eye)	Disruption of thyroid homeostasis (other than hypothyroidism)
Endocrine cancers (thyroid, thymus, and other endocrine organs)	Eve problems
other chronic B-cell leukemias)	Bone conditions
Other myeloid diseases (including myeloproliferative neoplasms)	Kidney and urinary disorders (including chronic kidney disorder, differences in kidney
Cancers at other and unspecified sites	function, nephropathy, and end stage renal disorder)
Infertility	Chronic skin disorders (including skin infections and changes in skin pigmentation)
Spontaneous abortion (other than after paternal exposure to TCDD, which appears not to be associated)	The committee used a classification that spans the full array of cancers. However, reviews for non-malignant conditions were conducted only if they were found to have been the subjects of epidemiologic investigation or at the request of the Department of Veterans Affairs. By default, any

health outcome on which no epidemiologic information has been found falls into this category.



Limited or Suggestive Evidence of No Association

Several adequate studies, which cover the full range of human exposure, are consistent in not showing a positive association between any magnitude of exposure to a component of the herbicides of interest and the outcome. A conclusion of "no association" is inevitably limited to the conditions, exposures, and length of observation covered by the available studies. In addition, the possibility of a very small increase in risk at the exposure studied can never be excluded. There is limited or suggestive evidence of no association between exposure to the herbicide components of interest and the following health outcome:

Spontaneous abortion after paternal exposure to TCDD



🖨 🛛 Military News

Defense Bill Would Add 3 New Diseases to Agent Orange Presumptive Conditions List

3 Dec 2020 Military.com | By Patricia Kime

Vietnam veterans suffering from several diseases that a scientific panel says are related to <u>Agent Orange</u> exposure won a hard-earned victory in Congress this week, with language included in the final defense policy bill that would grant them disability benefits.

If signed into law, the measure would give roughly 34,000 veterans diagnosed with hypothyroidism, bladder cancer or Parkinsonism access to disability compensation and health care services.

Not included in the bill is hypertension, a condition that the National Academies of Sciences, Engineering and Medicine linked to Agent Orange in 2018. Hypertension, or high blood pressure, is common among the elderly and, if included, would have added more than 160,000 veterans to VA disability rolls in the next 10 years at an estimated cost of \$11.2 billion to \$15.2 billion.

21-0107

Iris Martin/Sunny Kao/Megan Troxell; Stanford

28-year-old with gender dysphoria, on androgen deprivation and estrogen for years. Bilateral orchiectomy performed.














Differential Diagnosis

- Sertoli cell nodule with/without germ cell neoplasia in situ (GCNIS)
- Gonadoblastoma
- Sertoli cell tumor

Sertoli Cell Nodule with GCNIS



Sertoli Cell Nodule with GCNIS

- Usually small (<0.5 cm)
- Expanded tubules with thickened basement membranes
 - Nested
 - Lined by immature Sertoli cells
- Neoplastic germ cells
 - GCNIS; not uniformly distributed
- Seen in phenotypically normal males with cryptorchid testes and germ cell tumors



Gonadoblastoma

- Variably sized
- Composed of 2 cell types
 - Germ cells with varied appearance, ranging from spermatogonium-like to GCNIS like
 - Immature sex cord cells
 - Nested growth with hyaline nodules or calcifications (Call-Exner-like)
- Almost always in patients with abnormal, dysgenetic gonads
- Potential for malignant transformation

Importance of distinguishing the two...

- Different patient populations
- Morphologic diagnosis
 - Sertoli cell nodule with GCNIS
 often misinterpreted as gonadoblastoma
- Clinical management
 - Higher likelihood of bilateral neoplasms in patients with gonadoblastoma
 - Bilateral gonadectomy