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Introduction to EHE and Current Management

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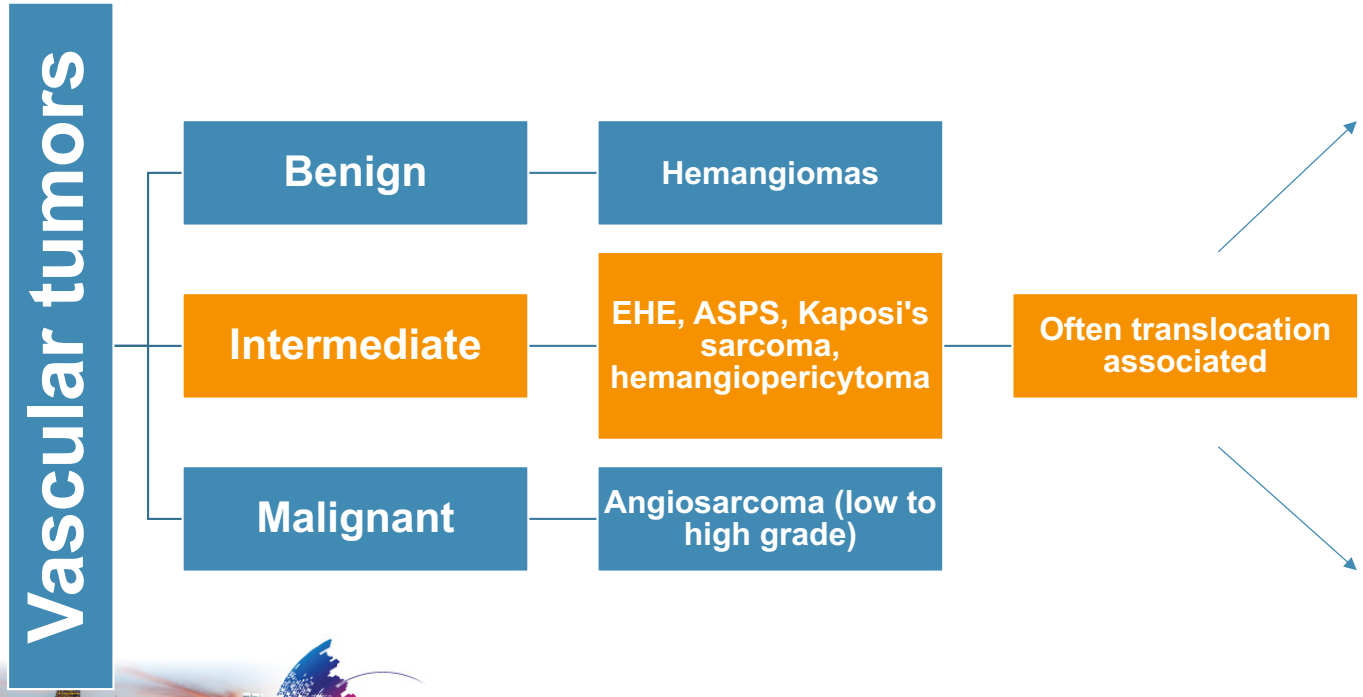
Overview of epithelioid hemangioendothelioma (EHE)

- EHE is a vascular sarcoma with conserved translocations arising in endothelial cells



WWTR1-CAMTA1 and YAP1-TFE3 translocations are pathognomonic for EHE

Key histologic features:
Endothelial cells in nests and cords
Fli-1 and CD31 expression typical
Chronic inflammation stromal components

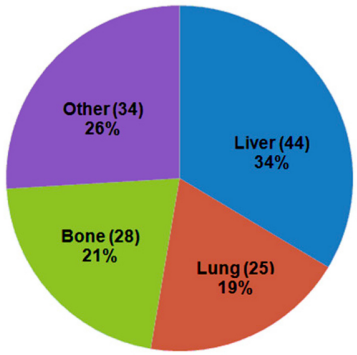
Rosenberg & Agulnik, Curr Treat Options Oncol 2018

Clinical presentation and behavior of EHE

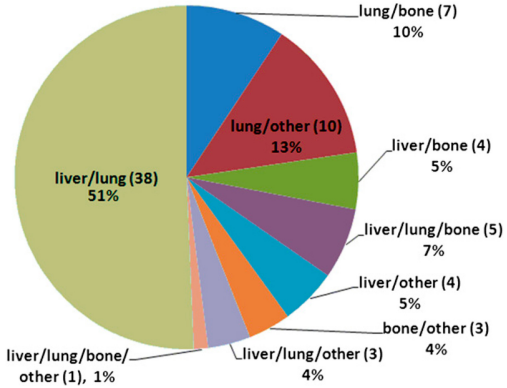
- Extremely rare – incidence of approximately 1 in a million
- Female > male predominance (4:1)
- Mean age 40.1
- Variable biology (indolent to rapidly progressing) and metastatic potential – not always histologic

Assess the individual patient's rate of growth and disease distribution before treatment decisions

Single-organ involvement (n=131)



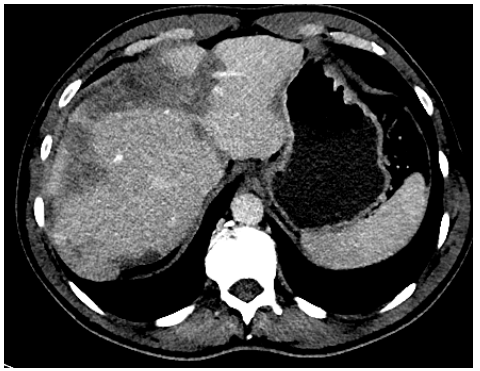
Multi-organ involvement (n=75)

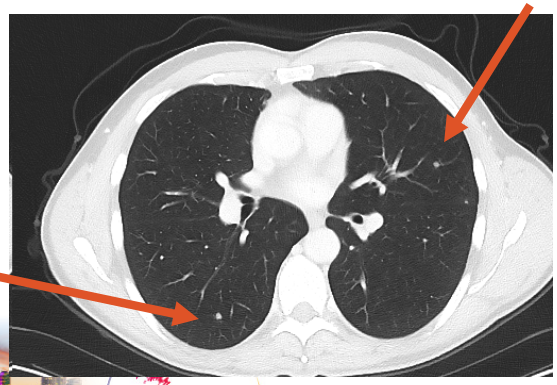


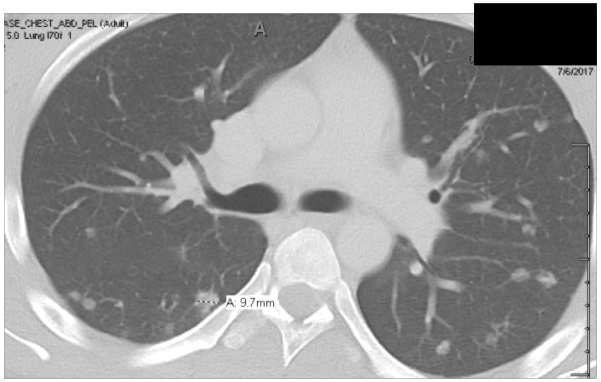
Lau et al, Chest, 2011

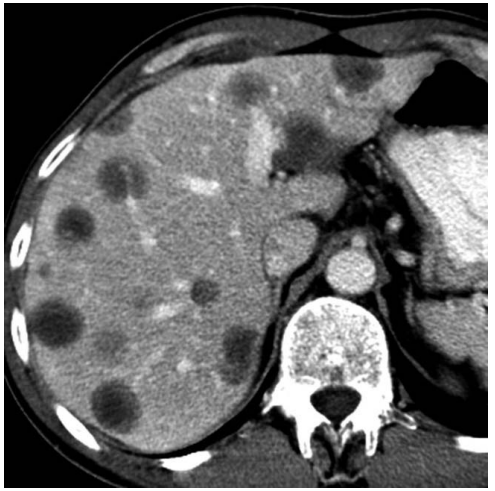
Representative EHE clinical vignettes

45 yo F undergoes CT imaging for LUQ abdominal pain and found to have innumerable pulmonary nodules, largest less than 2 cm in size, and discrete cystic appearing lesions in the liver, possible hemangiomas. Biopsy confirms diagnosis. Repeat imaging 6 months later shows no growth in any lesions.









Representative EHE clinical vignettes

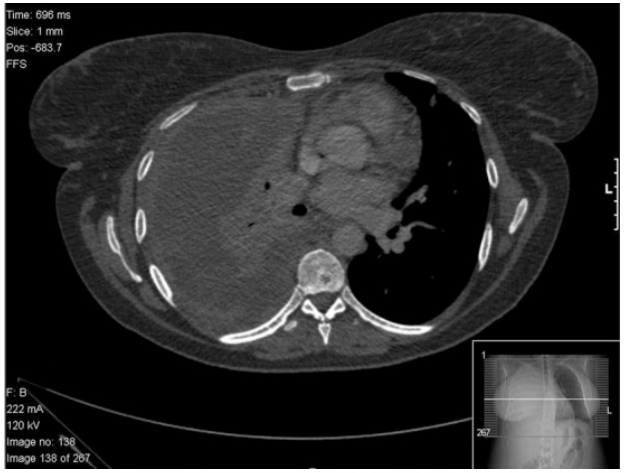
- Patients can have stable disease without progression for years (up to 30!), 5 year OS >81%
- Most patients eventually convert to more aggressive state
- Case reports of spontaneous regression
- Poorly understood impacts of hormones (estrogen), inflammation, immunity
- Liver transplantation can be curative for liver-only EHE (27% RR, n=59) but significant risk/potential toxicity

Lau et al, Chest, 2011
Makhlouf et al, Cancer 1999

Representative EHE clinical vignettes

- 55 yo M presents with severe back pain, imaging reveals multiple lytic lesions in the spine. Nuclear bone scan shows additional sites of disease in numerous other bones. Also found to have diffuse bilateral ground glass changes in the lungs bilaterally with consolidation concerning for right lung pleural involvement. Chemotherapy initiated but patient developed respiratory failure within several weeks and hospice/comfort care was initiated.

- Pleural and bone involvement is particularly indicative of rapid progression and poor prognosis.
- Rule out angiosarcoma (fusion).



My treatment algorithm: EHE

Disease status	Treatment Options	Surveillance
Solitary site of disease (ie liver only)	Resection (SOC) **Local ablative procedures** Consider liver transplantation eval	After resection image site of disease every 4-6 months for first couple years then less often
Widely metastatic, unresectable (liver/lung, lung only)	Surveillance **Local therapy for progressing clones** Systemic therapy for widespread progression	Serial scans of disease locations: CT chest, MRI liver, bone scan every 4-6 months Once indolence established can decrease intervals of scans
Limited progression of metastatic/unresectable disease	Consider local ablative therapies particularly if only one or two lesions are changing in size	Scans of disease locations every 3-4 months
Widespread progression, new lesions, or high risk locations (ie pleural, bone)	Systemic treatment recommended (clinical trials preferred if available) Targeted radiation or ablative therapies to symptomatic bone lesions	Scans every 2-3 months on therapy

Systemic treatment options: EHE

- Due to rarity, majority of data is from case reports and series (<100 pts), anecdotes
- First EHE specific clinical trial recently completed accrual, MEK inhibitor based on downstream targets of the conserved fusion – final results still pending
- Most therapies are stabilizing at best, rare long term responses
- Ongoing international collaboration to pool retrospective data and treatment experiences
- Interest and awareness through patient advocacy groups are critical to advance the field

Pazopanib
Sorafenib
Apatinib
Bevacizumab monotherapy
mTOR inhibitors
Trametinib

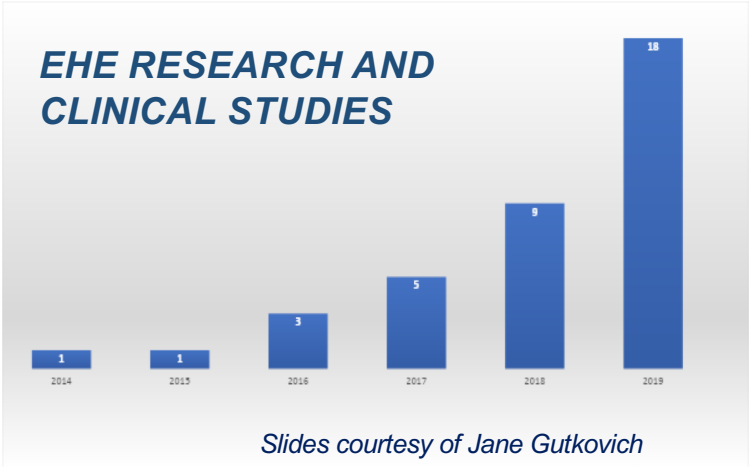
Thalidomide/Lenalidomide
Checkpoint inhibitors
NSAIDs
Metronomic cyclophosphamide

Liposomal doxorubicin
Doxorubicin combinations
Single agent paclitaxel
Carboplatin/paclitaxel

Rosenberg & Agulnik, Curr Treat Options Oncol 2018

Patient organizations as advocates for rare diseases

- Research foundation and Facebook page (over 1000 members) helps EHE patients network and get to expert centers
- Opportunities for sufficient numbers for trials or at least retrospective experience
- Private philanthropy and fundraising has funded 2 $1M grants for EHE research in 2019
- First EHE-specific clinical trial (2017)
- First genetic mouse model created (2019)



Slides courtesy of Jane Gutkovich

Role of the immune system in EHE

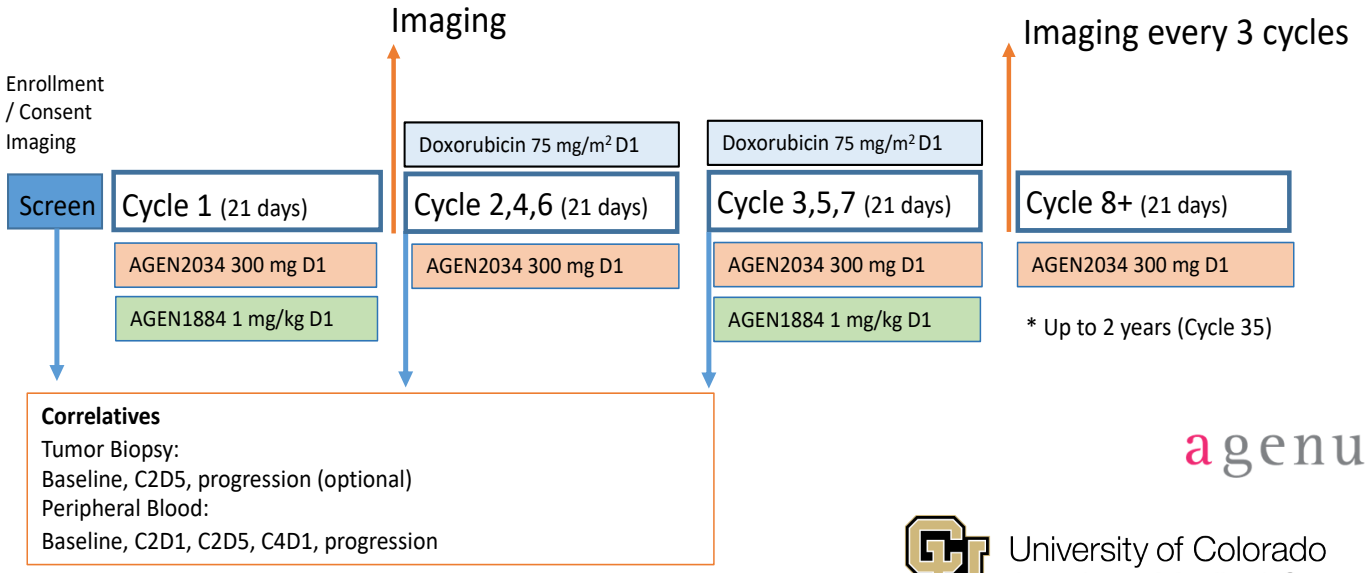
- Prolonged indolence with abrupt breakthrough fits paradigm of immune suppression…equilibrium… escape
- Other sarcomas with similar clinical behavior have responded to immune therapies (alveolar soft part sarcoma)
- Occasional sporadic regressions without treatment
- Ablation/IRE or chemo -> increase antigen presentation -> abscopal benefit?
- Very little known on immune infiltrates in EHE tumors – but high stroma…
- Low mutational burden (translocation driven)
- Anecdotes of responders to checkpoint inhibitor therapy

De Baere et al, Eur J Cancer, 2018

Doxorubicin plus dual checkpoint blockade

Hypothesis: Doxorubicin will increase antigen presentation/T cell expansion in combination with checkpoint blockade

Open Label, single arm, single center, investigator-initiated Phase II for up to 28 evaluable patients with advanced/metastatic sarcomas, anthracycline naïve, max of 1 prior therapy – **progressing EHE eligible**



Opening 1/2020 –
CU Cancer Center
NCT04028063, PI: Wilky

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Summary

- EHE is a highly rare sarcoma, with incredible biologic diversity in terms of organ predilection and progression of disease
- Don’t over-treat indolent phase EHE – systemic therapy is palliative
- Progression-free survival appears to be improved with locally directed therapies to progressing clones – avoids use of marginally effective systemic therapy
- The immune system/inflammation is likely involved in EHE biology – but details are unknown, and role of immunotherapy just beginning to be explored
- Patient advocacy groups are critical to moving forward with better research opportunities and improved understanding of the disease

Thank you and questions!

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