What’s new in Pediatric Dermatopathology?

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Dermatopathology workforce in the U.S.: a survey

Surveyed practicing fellows of the ASDP (437/913)
Most common areas identified as training gaps:
  - coding/billing (47%)
  - biostatistics (38%)
  - pediatric clinical dermatology (27%)
  - electron microscopy (27%)
Spiny papules
Trichodysplasia spinulosa

- Spiny follicular projections
- Central face characteristic
- Characteristic histology:
  - Dilated plugged follicles, proliferative IRS, enlarged trichohyalin granules
Trichodysplasia spinulosa

- TS-associated polyomavirus
- Immunocompromised, transplant patients
- TSPyV sequenced July 2010 (#8 human polyomavirus)


Polyomaviruses – what’s new?


- 14 species known in humans, 7 detected in the skin
- 1\textsuperscript{st} discovered was MCPyV (2008)
- Only MC, TS, and HPyV6 and V7 have been definitively associated with skin disease
  - V6 and V7 with pruritic skin disorders
- HpYV9, V10, V13 unclear –? role in colon cancer and nephropathy post renal transplant
  - Compared skin of liver transplant patients (benign and pre-malignant lesions) and healthy skin of immunocompetent adults
  - Viral findings in premalignant v benign skin were ALIKE
  - Speaks AGAINST a role of the HPyVs in SCC development
Painful red nodules
Pertinent history

On BRAF inhibitor for brain stem glioma
BRAF inhibitor-induced panniculitis
Vemurafenib-induced neutrophilic panniculitis


BRAF inhibitors – expanding role

Melanoma
Thyroid
Colorectal
Non-small cell lung
Brain
Vermurafenib in Langerhans cell histiocytosis


BRAF V600E documented in over half of tested
Langerhans cell histiocytosis lesions
Solitary pink bump
Sophie Spitz (1910-1956)
MELANOMAS OF CHILDHOOD *

Sorrel Soter, M.D.
(From the Pathology Laboratories of the Memorial Hospital, New York, N.Y.)

It has become apparent over a period of years that even when a histologic diagnosis of malignant melanoma has been made in children the clinical behavior rarely has been that of a malignant tumor. The disparity in behavior of the melanomas of adults and children, despite the histologic similarity of the lesions occurring in the different age groups, is obviously a matter of fundamental importance and the following questions immediately arise: Does the histologically malignant melanoma of children differ in any structural detail from that of adults? Can the clinical behavior of these lesions be predicted from their histologic structure? What, if any, are the factors known to influence the clinical behavior? Should the melanomas of children be treated any differently from the melanomas of adults?

MATERIAL

In a search of the files of the Memorial Hospital for instances of malignant melanoma in children, it soon became apparent that the diagnosis had been made with far greater frequency 20 or more years ago than in the past decade. This difference was quickly accounted for in the usual structure of the benign pigmented nevi of children as contrasted with that of the benign nevi of adults. In more recent years, the criteria for the diagnosis of malignant melanoma had become clarified to the extent that histologic features of the nevus of childhood, formerly regarded as stigmata of malignant change, were no longer so considered. However, there remained a group of cases in which a diagnosis of malignant melanoma seemed histologically sound. Over a period of years, the qualification has been added to reports of such lesions that they probably would not behave as malignant tumors. In order to distinguish these lesions both from the malignant melanomas of adults and the unequivocally benign nevus of childhood, the term "juvenile melanoma" has been adopted. The term "melanoma" in this paper, as in common usage, has been applied only as an abbreviation for malignant melanoma.

The material for this study is comprised of 13 cases† diagnosed histologically as juvenile melanoma during the past 13 years and occurring in children ranging in age from 18 months to 12 years. For

* Received for publication, June 4, 1947.
† Submitted from the Malign Tumor Service of the Memorial Hospital.
Dr. Spitz’s observation

“It has become apparent over a period of years that even when a histologic diagnosis of malignant melanoma has been made in children the clinical behavior rarely has been that of a malignant tumor.”
Dr. Spitz’s paper

17 “adults” with melanoma (age 14-17)
  ◦ 12 died within 6-18 mo

13 children (age 2-12) with “juvenile melanoma”
  ◦ 1 died

50 benign nevi in children

Conclusions
  ◦ Histologic similarities to adult melanoma BUT
  ◦ These “juvenile melanomas” are histologically distinct AND
  ◦ Behave in a clinically benign fashion
Clinicians are confused...
(overheard in the workroom)

- Is a Spitz nevus benign?
- Do I need to re-excise it? How wide?
- What if the report says “atypical”? 
- What is this “AST”? 
- But the patient is a kid! It’s not melanoma.
- But the patient is an adult! It’s not a Spitz nevus.
- Spitz nevi turn into melanoma.
- SLNB will tell us what it really is.
- Molecular studies will tell us what it really is.
Pathologists are confused...


30 melanocytic lesions
  ◦ Atypical Spitz nevi and metastasizing Spitzoid tumors/melanomas
  ◦ **Known clinical outcome**

Reviewed independently
  ◦ 10 dermatopathologists
  ◦ Blinded to clinical data
  ◦ Put in 1 of 5 categories : SN, ASN, MM, NUB, other
17 Spitzoid lesions: no clear consensus

- Only 1 case where 6 or more pathologists agreed on a single category
- Some fatal lesions were categorized by most observers SN/ASN
- 7 or more pathologists scored 13 lesions as melanoma
Almost 20 years later... still confused


M-Path study database

187 pathologists, 240 cases, 8976 independent diagnostic assessments

- 90% used Spitz-related terminology
- significant variation in which lesions were diagnosed as “Spitzoid” and in treatment recs
- “no further treatment” $\leftrightarrow$ “wide excision of 10 mm or greater”
- no category captured more than 50% of responses
- reported less confidence in these lesions compared to other melanocytic lesions
Ultimate **patient outcome** is still best diagnostic tool

Molecular studies will help us identify high risk lesions/aggressive clinical behavior
Not new: Sentinel lymph node utility


67 patients with atypical Spitz tumors (median age 23.7 years)

57 had a SLNB performed
- 27 (47%) positive
- SLNB-positive cases had a significantly lower mean age than SLNB-negative cases (17.9 vs 28.7 years)
- All 27 patients with a positive SLNB were alive and disease free with median follow-up of 43.8 months
- One patient who did not receive a SLNB developed recurrent disease with regional and distant metastases
Conclusions

- ASTs do not appear to behave like conventional melanoma
- High incidence of microscopic lymph node deposits in SLNBs, but patients have a favorable prognosis
- No role for SLNB in diagnosis/management
- Several similar subsequent studies
Promising molecular data: 9p21 deletion

- 2 groups: AST with chromosomal copy number changes v. conventional MM
- All AST had 1 or more chromosomal aberration
- 2 AST with homozygous 9p21 deletion developed brain mets, 1 death
- 21 conventional MM – 3 deaths

- 31 ASTs with hetero loss of 9p21 → no distant mets
- 30 ASTs with homo loss of 9p21 → looked “worse” histologically, more aggressive clinically
Promising molecular data: 9p21 deletion


- 246 patients
- 13% had “positive” FISH
- F/U data in 85 patients: 2 had recurrence, 1 with distant met, both with homozygous deletion at 9p21

- “Subgroup of patients with homozygous deletions in 9p21 is at higher risk for aggressive clinical behavior, but prognosis seems considerably better than similarly staged conventional melanoma”
TERT promoter mutations


- 56 patients
- available follow-up data, mean 32 months: 4 died
- TERT-p mutations in those 4 cases
- biallelic CDKN2A deletion, biallelic PTEN deletion, BRAF/NRAS mutations, and kinase fusions also evaluated
ALK fusions


- 17 patients
- **HISTOLOGY**: polypoid lesion, plexiform growth pattern, intersecting fascicles, fusiform melanocytes


- 32 lesions
- **HISTOLOGY**: exophytic lesions, large nests of fusiform cells in elongated and radially oriented nests, infiltrative at periphery
ALK fusions


Toward a molecular-genetic classification of Spitzoid neoplasms

- 11p amplification and/or HRAS mutation: typical morphology, benign clinical behavior
- Bap-1 loss and BRAF V600E mutation: typical morphology, benign clinical behavior
- Translocations of various oncogenic kinase drivers occur across the spectrum of Spitzoid neoplasms: implications for therapy
- Lesions with TERT promoter mutations exhibit more aggressive clinical course: additional marker for aggressive behavior
- FISH can identify lesions with increased risk for metastasis and death: homozygous deletion of 9p21
Last case: Another solitary pink bump
Special stains for microorganisms and cultures negative
Idiopathic Aseptic Facial Granuloma

- Young children
- Solitary firm pink plaque on the cheek
- **Granulomatous histology**, infectious work up negative
- ? Form of infantile/childhood rosacea
  - Reported improvement with “anti-inflammatory doses” of antibiotics, metronidazole, Ivermectin
  - Histologic features c/w granulomatous rosacea