What’s new and Interesting in Pediatric Dermatology?

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Treatment of infantile hemangiomas

Propranolol: not “new”, but changing
Propranolol

- Off-label use for infantile hemangiomas since 2008
- Since 2014, FDA approved for first-line therapy in high risk IH
- Has largely replaced systemic steroid therapy for high risk IH
Hemangeol®

Pierre Fabre Dermatologie

FDA approved March 2014
  ◦ Propranolol hydrochloride
  ◦ 460 infants age 5 weeks to 5 months, proliferating IH, treated for 6 months
  ◦ 60% had complete or near-complete resolution (4% with placebo)

Most common adverse reactions
  ◦ Sleep disturbance, V/D, aggravated respiratory infection symptoms

Serious reactions
  ◦ Hypoglycemia, bradycardia, hypotension, bronchospasm, worsening of CHF, possible increased stroke risk in patients with PHACE syndrome
Potential dosing errors

Generic propranolol hydrochloride:
- 4 mg/mL OR 8 mg/mL suspension (20 or 40 mg per 5 mL suspension)
- 1-3 mg/kg/day divided BID

Hemangeol:
- 4.28 mg/mL, supplied with graduated syringe, single specialty pharmacy
- dose calculated in mL/kg
- Start 0.15 mL/kg BID and increase weekly for 3 weeks to equivalent of 3.4 mg/kg/day

Over-dosing errors more frequent with generic form

Broadening of clinical indications for treatment
Pre-treatment and treatment protocols

  ◦ “Conservative”

  ◦ “Much variability”

Baseline BP (EKG or echo if clinically indicated by history)
If normal, start 1mg/kg/day divided BID
Clinical F/U and recheck of BP in one week
If normal and baby well, increase to 2 mg/kg/day, divided BID
F/U 1 month after starting medication
Can increase to 3mg/kg if poor response
Typical treatment duration is until age 12 months (“outgrow” dose)
Specific parental precaution: Hold drug for illness/vomiting (hypoglycemia → seizure)
Topical therapy

Timolol maleate 0.5% GFS (gel-forming solution) QD-BID
- Thin, superficial hemangiomas
- eyelid, lip, thin skin
- “for those who want to treat…”
- Survey results indicate timolol is used very frequently with variable protocols and monitoring

Propranolol 1% cream
- pyogenic granulomas (nail bed; medication reactions)
- promotes cutaneous wound healing (diabetic mice)
- no suggested protocol for IH
Expanding role for beta-blockers

Hepatic hemangioma, hemangioendothelioma
Tufted angioma and Kasabach-Merritt syndrome
Poor response in congenital hemangiomas
Polyomavirus
Trichodysplasia spinulosa

TS-associated polyomavirus

Transplant patients, others

Virus sequenced July 2010 (#8 human polyomavirus)


HPyV9 recently identified (unknown pathogenicity) – renal transplant recipients
Trichodyplasia spinulosa

Spiny follicular projections
Central face characteristic
Dilated plugged follicles, proliferative IRS, enlarged trichohyalin granules

Treatments reported:
- oral valganciclovir
- topical cidofovir
- shaving+tazarotene
- topical acyclovir + other agents
- modification of immunosuppressant therapy
Medication reaction
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
Treatment

Continue drug

Analgesics, Anti-inflammatories
Atypical Spitz neoplasms, evaluation, and SLNB
Sophie Spitz (1910-1956)
MELANOMAS OF CHILDHOOD *

Edward Sorensen, 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 15 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 nevi 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, 1942.
†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...

Is a Spitz nevus really benign?

☐ Then do I need to re-excise it?

☐ How wide?

☐ What if the report says “atypical”? What is an “AST”? Clinical presentation, age, anatomic location important?

Is there a relationship between atypical Spitzoid lesions and melanoma?

Is SLNB necessary or recommended?
Pathologists are also 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

Since 1999, better IHC, FISH, CGH

But

Ultimate *patient outcome* is still best diagnostic tool
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 of this study

- 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
More similar data

JAAD January 2015
Massi, et al.: Atypical Spitz tumors in patients younger than 18 years
50 patients; 1 fatality
All lesions were histologically worrisome
  ◦ Large size, poor maturation, nuclear pleomorphism, etc.
  ◦ Numerous deep mitoses (higher mitotic rate in younger patients)
FISH studies did not distinguish AST from MM
SNLB showed no clinical benefit
Do molecular studies help?

- 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
Do molecular studies help?


- 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”
For now...

Nomenclature
- Spitz nevus
- “so-called atypical Spitz tumor one hand, Spitzoid melanoma of childhood on the other”
- Spitz’s “Benign juvenile melanoma”
- Proceed with caution – fatalities occur

Molecular abnormalities seem to be common in ASTs, but their implications are not clear.

CGH and other molecular studies will likely become faster, more affordable, more helpful.

The use of SLNB is not supported in atypical Spitzoid lesions of childhood.
How I counsel parents and clinicians

Most pediatric Spitz nevi are just that: benign nevi

“Histologic variant” – may in fact be a unique entity

Malignant melanoma before puberty exceedingly rare, but reported

Some melanomas can show “Spitz-like” histology

SLNB does not aid in diagnosis and likely has no clinical benefit in AST management

If you biopsy, remove the entire lesion
  ◦ Minimize recurrence risk and “scarier” histology later
  ◦ Give pathologist an opportunity to examine the entire lesion

Know your dermatopathologist
Sirolimus/rapamycin
Sirolimus/rapamycin (Rapamune®)

Inhibits IL-2 via binding of FKBP12
- Sirolimus-FKBP12 complex binds mTOR → blocks T and B cell
- Tacrolimus-FKBP12 complex inhibits calcineurin

Potent immunosuppressive and antiproliferative properties

FDA approved 1999 (post-transplant organ rejection prevention)

Other uses
- Cardiac angioplasty stents
- Kaposi’s sarcoma and lymphomas
- Psoriasis, lichen planus
- Symptom complex of tuberous sclerosis
  - Renal angiomyolipoma, giant cell astrocytoma, lung lymphangiomyomatosis
Angiofibromas of TS


- Angiofibromas show increased expression of angiogenic factors (VEGF) and mTOR overactivation
- Inhibition of mTOR pathway \(\rightarrow\) decreases VEGF and endothelial cell proliferation
- Role in angiofibromas and diffuse lymphangiomatosis/complicated lymphatic tumors
Treatment considerations

Large molecule, difficult to formulate in ointment form

Formulations and treatment protocols vary

Oral solution (1 mg/ml) used topically is probably most practical
  - Compounding tablet into ointment less feasible: stability, efficacy, cost

Irritation and burning sensation can be treated with low potency topical steroid

Systemic absorption minimal, no level monitoring required
New concepts in acne therapy
Isotretinoin dosing and relapse

- Current standard: 120-150 mg/kg

- Blasiak, JAMA Derm 2013: Doses of 220 mg/kg or more = significantly lower relapse rate at 1 year, no increase in adverse side effects

- Zeitany, JAAD 2016: High dose is more cost effective

- “high and dry” vs. “low and slow”
Drum roll....

Adapalene (Differin®) is available OTC!

0.1% gel
15 g = $12
45 g = $29
New treatments for atopic dermatitis

- Dupilumab (Dupixent®)
- IL-4 (and IL-13) receptor antagonist
- Regeneron (“Reinventing invention”)
- Approved March 2017 for moderate-severe AD in adults not controlled on RX topical therapy
- 1st biologic approved for treating AD
- 300 mg SQ q week or q 2 weeks; 300mg/2mL single-dose prefilled syringe
- With or without topical steroids
- Studies in children ages 6-11 and 12-17 ongoing
  - AD appears to be more Th-2 driven in children v. adults
  - Pruritus is most improved parameter (skin lesions, anxiety, depression, quality of life)
New treatments for atopic dermatitis

- Crisaborole ointment (Eucrisa®)
- FDA approved Dec 2016, mild-moderate AD in patients 2 years and older
- 1st new RX drug for AD in over 10 years
- Non-steroidal, PDE-4 inhibitor
- Specific MOA in AD “not well-defined” – Pfizer
- Appears to be safe and moderately effective
New (and silly) thing kids do
Clinical photo attached!
“Invisible”/UV tattoo reaction


Local granulomatous tissue reaction to components of UV tattoo ink

Melamine, other substances

Fluoresce with black light; invisible in natural light

- Becoming more popular
- Clubs, parents, bosses...
Salt-ice challenge

Salt placed on skin prior to ice cube
Lowers temperature more than ice alone
Challenge is to hold on as long as possible (and video or post photos, of course!)
Pain, frostbite-like burns, persistent dyspigmentation, nerve damage
Other social media trends
Other social media trends

Eraser ("ABC") challenge
Other social media trends

Eraser (“ABC”) challenge
Other social media trends

Eraser (“ABC”) challenge

Kylie lip challenge
Treat the skin gently! (and wear sunscreen).
Thank you!