Genetic Aberrations Confirmed by Immunohistochemistry on Skin Biopsies

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UBC Faculty Disclosure
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- employee of Vancouver Coastal Health

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Objectives

- for discussion today:
  - identification of familial cancer syndromes
  - treatment of metastatic or locally advanced skin cancers

- outside scope of discussion -
  gene-product IHC for tumor diagnosis:
  - cutaneous lymphomas, Eg. bcl-2
  - post-breast-Ca angiosarcoma *MYC* amplification

no reproduction please

Advantages of Skin Biopsy

- like blood, readily accessible
- most frequently biopsied tissue
  - 18,000 / 45,000 – 40 %
- usually tumor tissue left over after diagnosis
- paraffin-embedded – available indefinitely

Muir-Torre Syndrome

- variant of Lynch syndrome described in ’67/’68
  - same mechanisms: MSI; MMR defects confirmed by Lynch in ’81
  - proportion different: in Muir-Torre 90 % due to *hMSH2*
- AD, same internal tumors as Lynch II:
  - colorectal adenoCa, endometrial Ca, genitourinary TCC
  - ovary, breast, upper GI, lung, CNS
- plus one or more sebaceous tumors of the skin
  - sebaceous tumor diagnosed 1st in 30 %
- same indication for colonoscopy $\pm$ TAH+BSO etc.

Skin Tumors Increased in Muir-Torre Syndrome

- sebaceous hyperplasia (non-definitional)
- sebaceous adenoma
- sebaceoma
- basal cell carcinoma with sebaceous differentiation
- sebaceous carcinoma
- keratoacanthoma with sebaceous differentiation
- usual keratoacanthoma (non-definitional)

Muir-Torre Clinical Definition

- 1 internal malignancy + 1 sebaceous tumor
- poor accuracy in detecting syndrome
  - + family Hx in only 50 % of clinically defined
  - 70 % of clinically defined are genetically confirmed
  - 50 % with sebaceous tumor and genetic confirmation meet clinical definition

IHC for MMR in Vancouver Coastal

- MSH2, MSH6, MLH1, PMS2
- 54 sebaceous neoplasms
  - 37 intact expression
  - 17 (32 %) abnormal
    - 16 MSH2/MSH6
    - 1 MLH1/PMS2
- all reported to clinician - ? outcome

Correlation of IHC with Somatic Mutation

- 93% accuracy in unselected series of 41 sebaceous tumors

- PPV of loss of MSH2, MSH6 or [MSH2 + MSH6] = 55- 65 %
- PPV of MLH1 loss = 90 %
- PPV of loss of [MSH2 + MLH1] = 100 %

Chhibber et al. Mod Pathol 2008;21(2)

- somatic mutation vs germline mutation
  - sebaceous tumors increase after organ transplant
  - proportion of somatic mutations increases after organ transplant

Correlation of IHC with Germline Testing

- population = 86 patients referred to genetics clinic for sebaceous tumor
- of 25 patients with germline mutations
  - only 14 (56 %) met clinical criteria for Muir-Torre S.
  - only 12 (48 %) met Amsterdam criteria for Lynch S.
- IHC abnormal in 13 / 16 of patients with germline mutation (81 % sensitivity)
- PPV of abnormal IHC for germline mutation = 37%
  - at least as cost-effective as IHC on colorectal Ca

Everett et al. JAMA Derm 2014;150(12)

Current Management after IHC on Sebaceous Tumor

- if IHC abnormal, confirmation of syndrome with
  - referral to Medical Genetics for germline testing
    and/or
  - defining personal / family history

- if IHC normal, further exclusion of syndrome:
  - if PMH/FH +, or multiple sebaceous tumors, then Medical Genetics

Other Cancer Syndromes with Skin Biopsies

- nevoid basal cell carcinoma syndrome – basal cell carcinomas
- tuberous sclerosis – angiofibromas
- Cowden syndrome – trichilemmomas
- hereditary leiomyomatosis and renal cell cancer – cutaneous leiomyomas

Nevoid Basal Cell Carcinoma Syndrome

- AD
- manifestations:
  - early multiple cutaneous BCCs, palmoplantar pits
  - keratocystic odontogenic tumor, medulloblastoma
- *PTCH* gene
- vismodegib = inhibitor of downstream pathway by blockade of SMO receptor

- mutation in all hereditary and sporadic BCCs
- IHC testing on BCC has no diagnostic or therapeutic utility

Tuberous Sclerosis

- distinctive cutaneous stigmata of multiple types, including angiofibromas
- retardation, seizures, CNS cortical hamartomas and tumors
- angiomyolipoma, rhabdomyoma, lymphangioleiomyomatosis

- *TSC1* – hamartin; *TSC2* – tuberin

- mTOR pathway inhibited by sirolimus (rapamycin) – clinically effective

IHC of Angiofibromas

- vast majority of angiofibromas sporadic and solitary
- 71 angiofibromas enriched for syndromic cases
- clinical definition of syndromic vs sporadic
- loss of hamartin and/or tuberin by IHC in
    - 21 / 59 (36 %) of syndromic
    - 0 / 12 sporadic

Fackler et al. J Cutan Pathol 2003;30(3)

- unlike Muir-Torre syndrome:
    - clinical definition is easy
    - proportion of syndromic skin tumors is low
  - less utility to testing

Cowden Syndrome (Multiple Hamartoma Syndrome)

- AD
- distinctive mucocutaneous stigmata of multiple types;
  most sensitive + specific = trichilemmomas
- internal neoplasms and hamartomas
  - breast Ca, fibrocystic disease; thyroid neoplasia
  - endometrial, colorectal, kidney Ca's
  - occ. Lhermitte-Duclos D. (dysplastic cerebellar gangliocytoma)
- *PTEN* gene, PTEN gene product
- downstream pathway mTOR inhibitor sirolimus (rapamycin) again clinically effective

IHC of Trichilemmomas

- most trichilemmomas sporadic and solitary
- 39 trichilemmomas enriched for syndromic
- clinical definition of syndromic vs sporadic
- loss of PTEN in:
    - 5 / 6 syndromic
    - 1 / 33 sporadic (? undiagnosed syndrome)

Al-Zaid et al. J Cutan Pathol 2012;39(5)

- clinical definition fairly easy in Cowden syndrome
  – benefit to IHC testing currently uncertain

Hereditary Leiomyomatosis and Renal Cell Cancer Syndrome

- rare - about 100 families worldwide
- AD
- manifestations:
  - variable number of cutaneous pilar leiomyomas
  - uterine leiomyomas, leiomyosarcoma
  - risk of renal cell carcinoma
- fumarate hydratase gene + gene product
- currently no molecular treatment, but possible utility of IHC in syndrome diagnosis

IHC of Cutaneous Leiomyomas

- most cutaneous leiomyomas sporadic and solitary
- 42 cutaneous smooth muscle neoplasms,
  enriched for syndromic cases
- clinical definition of syndromic vs sporadic

- IHC for loss of fumarate hydratase
  - 85 % sensitivity for syndrome
  - 75 % specificity (? undiagnosed syndrome)

Llamas-Velasco et al. J Cutan Pathol 2014;41

IHC of Skin Biopsies for Diagnosis of Family Cancer Syndromes

- not useful if genetic defect has the same frequency in syndromic and sporadic cases (BCC)
- screening test - does not correspond precisely to presence of a germline genetic defect
- useful for Muir-Torre because:
  - clinical definition is poor
  - cutaneous findings are meager and relatively non-specific
  - prevalence of syndromic sebaceous tumors high relative to sporadic sebaceous tumors
- utility variable in other syndromes depending on
  - ease of clinical diagnosis
  - population prevalence of syndromic vs sporadic skin tumors

Treatment of Melanoma

- pathogenic *BRAF* mutation in about 60%
- transient remission with treatments
  - anti-BRAF (vemurafenib, dabrafenib)
  - downstream target of MAP-kinase pathway (trametinib)
- identification of most common mutation of *BRAF*, V600E mutation, by IHC for gene product

Weakness of IHC for *BRAF* Mutation

- anti-V600E-BRAF identifies the protein product of only about 80% of *BRAF* mutations:
  - another 10% V600K mutations
  - final 10% a variety of other mutations
  - all *BRAF* mutations potentially responsive to MAP-kinase pathway inhibitors

- positive IHC result sufficient for treatment;
- negative result needs PCR to exclude *BRAF* mutations

Merkel Cell Carcinoma

- uncommon skin cancer, sun-exposed skin of elderly
- frequent distant metastasis, high mortality
- Merkel cell polyomavirus pathogenic in majority
  - present in 80% of MCC's (fewer in Australia)
  - antibody against MCPV large T antigen in FFPE tissues

IHC for MCPV for diagnosis ?

- MCPV DNA and antigen present in only 80 % of MCC
- MCPV DNA variably present in many other skin tumors, but antigen usually undetectable by IHC
- DNA and antigen absent in other potentially metastatic small-cell neuroendocrine Ca’s

IHC for MCPV for therapeutic decisions ?

- Current multicentre US NCI clinical trial for MCCs containing MCPV
- infusion of autologous T-cells that are targeted against MCPV-oncoprotein

Summary

- skin is:
  - readily accessible
  - frequently biopsied
  - a source of leftover tumor tissue for special studies
- skin tumors provide insights into:
  - family cancer syndromes
  - treatment options for advanced skin cancers
- future work:
  - family cancer syndromes: PPVs and cost effectiveness
  - evolution alongside therapeutic targets