

Uncommon Histiocytic disorders

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Histiocytic disorders

- Histiocytes -important cells of the immune system
- Histiocytoses –disorders due to excess accumulation of histiocytes
- Each disorder is defined by the major histiocyte present
 - LCH =accumulation of Langerhans cells
 - HLH =accumulation of activated macrophages and T-cells

Uncommon Histiocytic disorders

“Non-Langerhans Cell Histiocytoses”

Uncommon histiocytic disorders
=Histiocytosis that is not LCH or HLH

The Spectrum of non-Langerhans Cell Histiocytoses-pediatrics

- Juvenile Xanthogranuloma
- Papular xanthoma.
- Generalized eruptive histiocytoma
- Benign Cephalic Histiocytosis
- Xanthelasma
- Xanthoma Disseminatum
- Progressive nodular histiocytosis
- Multicentric reticulohistiocytosis
- Erdheim-Chester Disease
- Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman Disease)

UCH

- Is it important to differentiate the different histiocytic disorders?
- Tend to need the same therapy
- Different responses to therapy
- Different outlook

Uncommon Histiocytic disorders

- Mainly involving skin –uncommonly may have systemic involvement
- Mainly skin but systemic is a major part of the clinical presentation
- Systemic involvement is the major component but skin may be involved

Cutaneous Histiocytoses

- **Juvenile and Adult Xanthogranuloma**
- **Benign Cephalic Histiocytosis**
- **Generalized Eruptive Histiocytosis**
- **Xanthoma Disseminatum**
- **Papular Xanthoma and Xanthelasma**
- **Progressive Nodular Histiocytosis**

Mainly cutaneous but important
systemic component

- **Multicentric reticulohistiocytosis**

Mainly systemic with skin as part of the spectrum

- Sinus Histiocytosis with Massive Lymphadenopathy (SHML)
(Rosai-Dorfman Disease)
- Erdheim –Chester disease

Juvenile Xanthogranuloma

- **Commonest of the non-LCH**
- **Skin but 4%-10% outside of skin**
- **outlook depends on extent of non-skin disease**

Juvenile Xanthogranuloma

- Benign proliferative disorder
Initiating events?
- Involutes spontaneously months -years
Reason for involution?
Inflammatory response?

JXG

Bimodal peak:

- ▶ young child –by far commoner
med age: 2 years
- ▶ 20-30 year age group—adult XG

Range 0----80 years

JXG-commonest presentation

Skin only (75%)

- Single skin lesion usually <4cm diameter
Giant JXG >4cm
- Multiple skin lesions

JXG

- The younger the child the more likely the skin lesions are to be multiple
- Single skin lesion –average age 2 years
Male : female 1.5:1
- Multiple skin lesions: average age 5 mo
M:F 9:1

Skin JXG

- Natural history –benign -spontaneous resolution
- Complete disappearance or may leave a scar
- Low relapse rate -7%

Systemic JXG

4-10% in different series

Freyer et al, J Pediatr 1996

n=36

- Isolated subcut or deeper tissues 12/36 (33%)
- Liver, spleen 8/36 (22%)
- CNS----Discrete/leptomeningeal 8/36 (22%)
- Lung 6/36 (17%)
- Eye /orbit 4/36 (11%)
- Other-- including bone and bone marrow

JXG

- **eye JXG---rare but potentially serious (vision)**
- **92% less than 2 years of age**
- **45% have no skin nodules**

N.B. early diagnosis

Ocular JXG

Screen eyes in high risk patients

All children < 2 years of age with multiple skin lesions should have an eye consultation every 3 months

JXG therapy –localized

- Surgery –most reliable therapy but is it necessary?
 - biopsy to make diagnosis
 - functional problem
 - cosmetic
 - adult XG
 - residual scar

JXG therapy –systemic disease

Like skin JXG, systemic disease can heal spontaneously

- ▶ Observation is reasonable in some cases --
?most?
- ▶ When to treat?
 - Organ dysfunction
 - Rapid progression
 - Widely disseminated disease?

Symptomatic JXG patients

- Systemic steroids
- LCH –like therapy

Combination of vinblastine and steroid

- Radiation therapy (CNS, eye)

JXG therapy

Stover DG, Alapati S ...Whitlock JA. Pediatr Blood Cancer 2008

- 10 studies -15 cases - 29 chemo regimens
- 12/15 received some form of corticosteroid
 - 9/12 showed some response SD-CR
- Second commonest -vinca alkaloid 15/29 regimens foll by MTX (9/29) and etoposide 6/29

Regimens included steroid and vinblastine had highest response rate -regimens without steroid --lowest response rates

“Seems reasonable to treat symptomatic systemic JXG with LCH type therapy”

Chemotherapy

Trial and error

- Decadron instead of prednisone
- 2-CdA for CNS and non-responding systemic JXG
- Methotrexate combinations
- Etoposide
- Interferon
- Doxycycline *Bastida J et al Arch Dermatol 2007*

JXG summary

- Uncommon condition
- Majority have solitary skin lesions that can be observed
- Systemic disease in 4-10% of patients
- Can cause serious morbidity (eye, CNS) or even death

Therapy –start with LCH type therapy
vinblastine /steroid except some CNS patients
(?Decadron, ? 2-CdA)

If poor response to up-front Rx –trial and error to see what works for a particular patient

Adult XG

- Usually single lesion
- Typically 20-40 yrs---up to 80 reported
- Pathology same as JXG
- Head and Neck –none on lower extremity
- Most do not spontaneously involute or if do regress very slowly
- Surgical excision more important in adults

Erdheim Chester disease

- Disease of adults
 mean age 53 years (7-84 years)
- Bilateral symmetrical thickening of the long bones
- >50% extraskeletal involvement
Kidney, retroperitoneal, skin, brain, lung,
 others

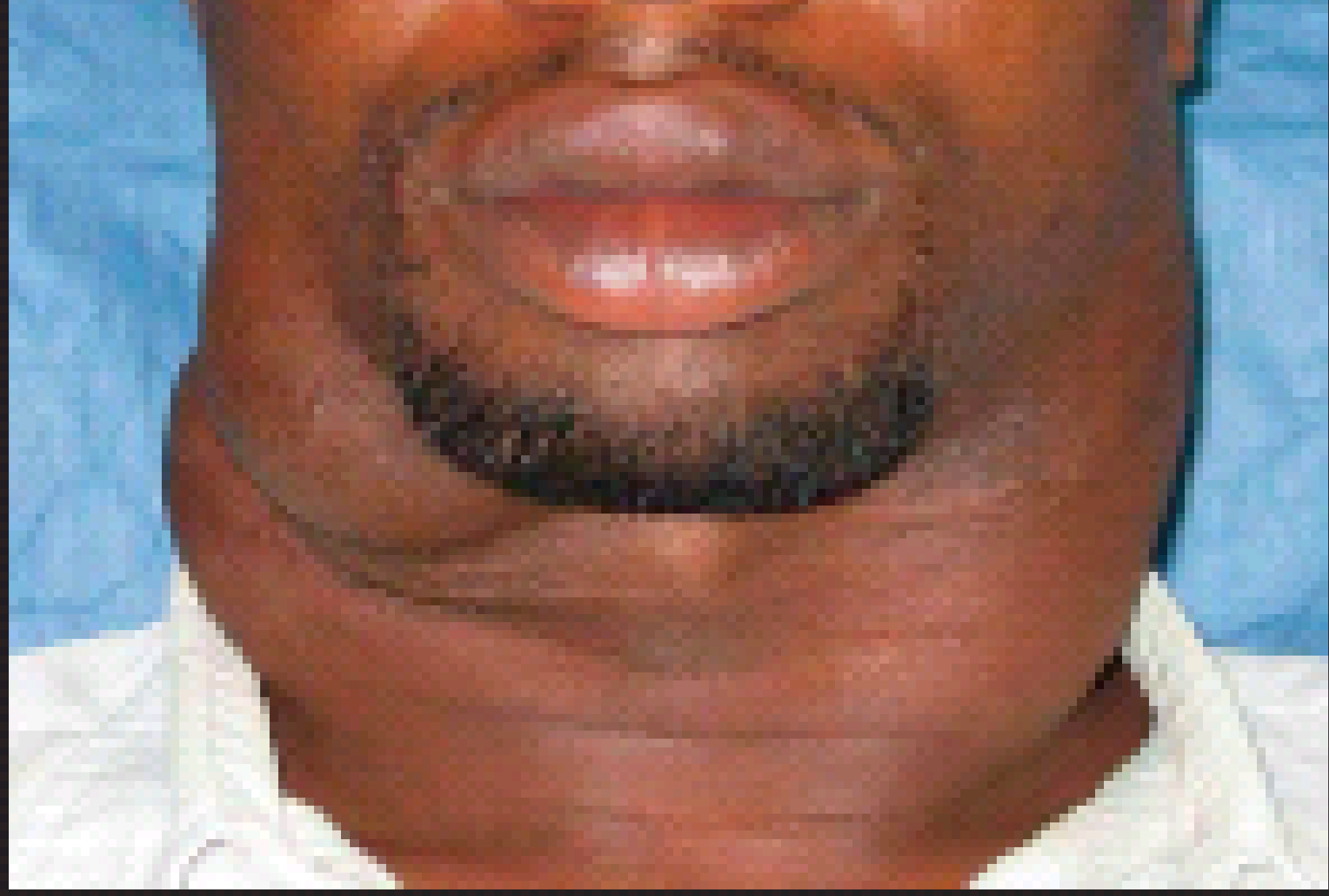
ECD- *Jaffe R, New Engl J Med 2008*

- Does not typically respond to steroid therapy
- Improvement or stabilization with a variety of therapies:
- Immunosuppression
- Irradiation
- High dose chemo with stem cell rescue
- Many combinations of chemo tried with varying success
- 2-Cda may be somewhat more effective than other agents
- 2 series with regression of radiographic findings and clinical improvement with interferon-alfa -2a

Haroche J et al Arthritis Rheum 2006;54:3330-3336, Braiteh F et al Blood 2005;106: 2992-2994

Rosai-Dorfman disease

- Young –mean age 20.6 years
- Bilateral painless enlargement of neck lymph nodes
- Enlarged lymph nodes can occur in other areas
- Fever, weight loss, night sweats



Rosai-Dorfman disease –
(Ref: Davis et al, Arch Otolaryngol, 131:2006)

SHML

- 43% disease other than lymph nodes
 - skin, soft tissue, bone, CNS,
eye, lung
- Very large nodes may compress
airway ---- respiratory obstruction

SKIN-ONLY RDD

- Isolated skin RDD very rare (~3% of patients)
- Older with preference for white females
- Usually benign course with spontaneous resolution in months
- assoc with lymphoma/solid cancers reported
- No reports of progression to systemic RDD

SHML

Mostly self –limiting, benign

- **5-11% die of disease**

RDD

- Clinical course usually indolent –for many years
- Spontaneous regression in majority

Like JXG systemic disease may regress without therapy
Newborn with anemia, low platelets and liver disease --better without therapy

Chow CP et al, Pediatr Blood Cancer 2008, 52: 415-417

- Does not usually threaten life or organ function
- 10% –progressive, may damage tissues
- Fatality is rare

RDD-why treat?

- CNS disease
- Manage symptoms
- Remove compression
- Correct disfigurement

Skin-only RDD

- Systemic , intralesional or topical steroids
- Surgical excision
- Chemo-alkylating agents
- Thalidomide *Wang KH et al, Br J Dermatol 2006;154:277-286*
- Superficial irradiation
- Isotretinoin-- immunomodulatory effects *Mebazaa A et al. Int J Dermatol 2007;46: 1208-1210*

RDD -therapy

- Wait and see
- Corticosteroids—prednisone /decadron
- Surgery
- Radiation therapy

RDD-chemotherapy

- VBL/prednisone *Dehner 2003*
 - VBL/Pred/6MP/MTX *Jabali et al, 2005*
 - VBL/pred/6MP *Ambati et al, 2008*
 - Dexamethasone/VBL *Stine et al, 2005*
 - Prednisolone alone-- symptoms resolved over 5 days to 6 months *Ocheni et al Eur J Cancer Care 2007*
- recurrence common following cessation of Rx

Imatinib(Gleevec) in RDD

Imatinib targets a number of growth factors including M-CSF-R
Inhibits development of monocyte-macrophage lineage

- ***Gebhardt C et al, Arch Dermatol 2009***

Patient with systemic RDD and no response after multiple other therapies Imatinib resulted in complete response

- ***Utikal J et al. Arch Dermatol 2007***

Systemic RDD -BM, Liver , spleen, skin -13 weeks Rx with Imatinib--
complete remission

- ***Montella L et al New Engl J Med 2004;104: 3038-3045***

--successful use of imatinib in cerebral LCH

Multicentric reticulohistiocytosis



Zelger et al, 2001

Multicentric reticulohistiocytosis

- Skin “coral bead” appearance nails
other
- Joints -symmetric destructive polyarthrititis
- Can effect nearly any organ
- May spontaneously remit but often after significant joint destruction

chemotherapy

- Methotrexate /pred ***Gourmelen 1991***
- Infliximab/MTX/pred ***Lee et al,2005***
- Infliximab/MTX ***Sellam, 2005***
- MTX low dose ***Rentsch et al,1998***

MRH

- All histiocytic disorders have increased production of chemicals which play an important role in the immune system
- If produced in excess causes damage, often severe
- One of these important chemicals = tumor necrosis factor alpha ($\text{TNF}\alpha$)
- Elevated cytokines include Tumor necrosis factor, IL-1, IL6, IL12, PDGF β

MRH--Therapy with TNF- α blockers

- Etanercept **yes** *Matejicka et al. Arth Rheum 2003; Kovach et al 20*
No *Lovelace et al, 2005*
- Infliximab (Remicaide) *Shannon SE et al J Rheumatol 2005, Kalajian AH, Callen JP Arch Dermatol 2008;144: 1360-66*
- Adalimumab *Shannon Se et al J Rheumatol 2005*

TNF-inhibitors combined with chemotherapy

- Etanercept plus prednisone, methotrexate

Lee MW et al Acta Derm Venereol 2004; 84: 478-9

- Suggestion that combination anti TNF plus chemo may give best results *Kalajian & Callen 2008*

Risk –Interfere with function of normal
immune system

Risk of infection and 2nd tumors

Bisphosphonate therapy

- Many of the disorders have bone and joint destruction as part of the picture
- Osteoclasts are cells which decrease bone formation
- Biopsy of LCH bone and non-LCH--histiocytes infiltrating in bone/joint have characteristics of osteoclasts
- Do blockers of osteoclast activity such as are used in osteoporosis help for histiocytic bone lesions?

Osteoclast inhibition

Zoledronic acid Rx in elderly patient with MRH-
improvement in skin lesions, stabilization of joint
erosion

Olendronate (Fosamax)plus chemo produced
marked improvement in joints and skin

Pamidronate and olendronate have been used
successfully in bone LCH

Multicentric reticulohistiocytosis- therapy

- Tumor necrosis factor inhibition
- Plus/minus chemotherapy
- Plus /minus bisphosphonate (pamidronate, olendronate)

Uncommon Histiocytic disorders

- Patient may not need therapy –clinical judgment needed!
- If do need therapy –?Surgery will work?
- If not -chemotherapy --start with least toxic combinations
- If poor response –trial and error
- Individual patients seem to respond differently
- New biologic agents may work