The differential diagnosis of arthritis in children

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Arthralgia/arthritis

- **Arthralgia**: pain in a joint

- **arthritis**: joint swelling

  and/or

  articular pain and limitation of motion

Diseases that can cause articular involvement

- Infectious
- Post-infectious
- Inflammatory
- Hematological
- Neoplastic
- Genetic
- Orthopedic

The group of pieces

- Medical history and physical examination
  - characteristics of articular involvement
  - extra-articular symptoms
- Laboratory examination
- Imaging
- Follow-up

Arthritis characteristics

- Persistent or transient
- Number and type of joints
- Symmetric or asymmetric
- Intensity of articular pain
- Fixed or migrant
- Swelling>pain or viceversa
- Sensitivity to NSAIDs
- Morning stifness
- Pain on loading
- Presence of enthesopathy

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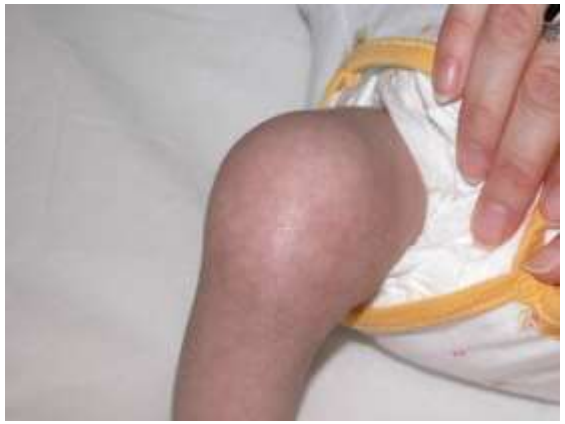
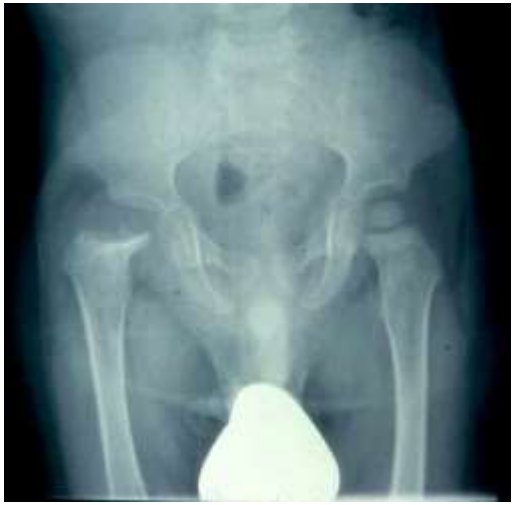
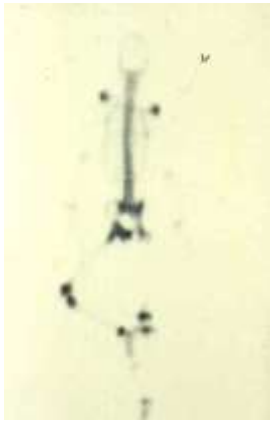
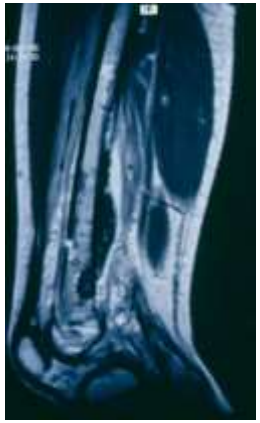
Septic arthritis









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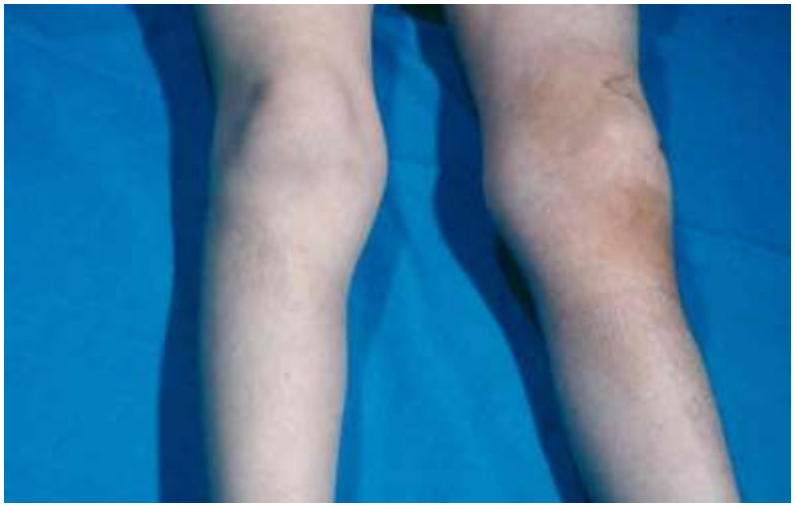
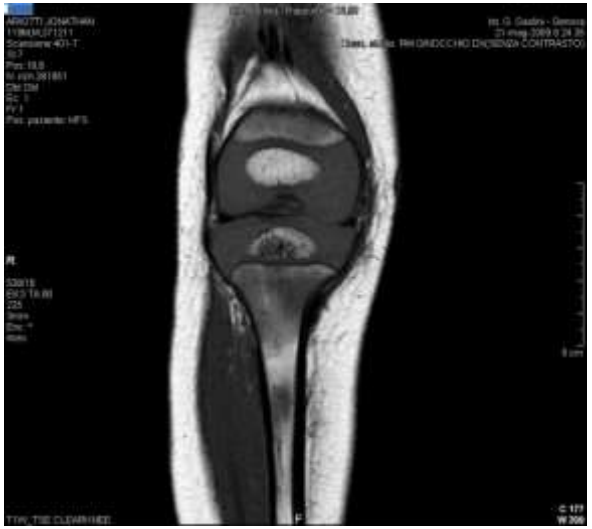
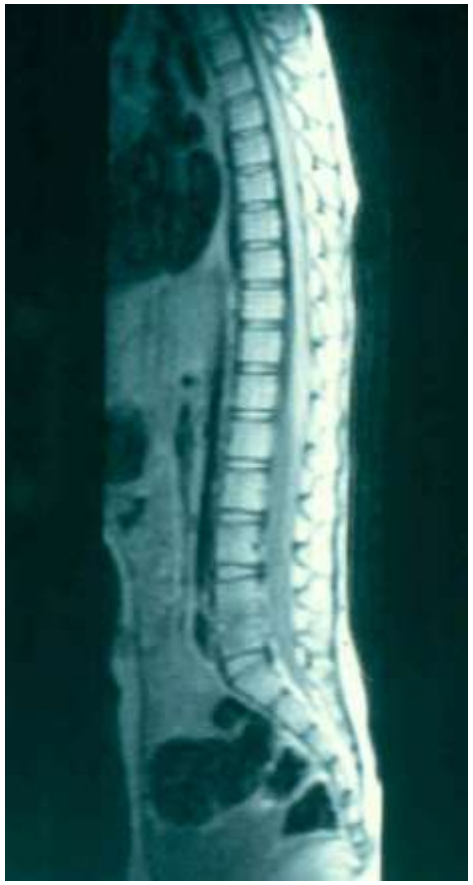
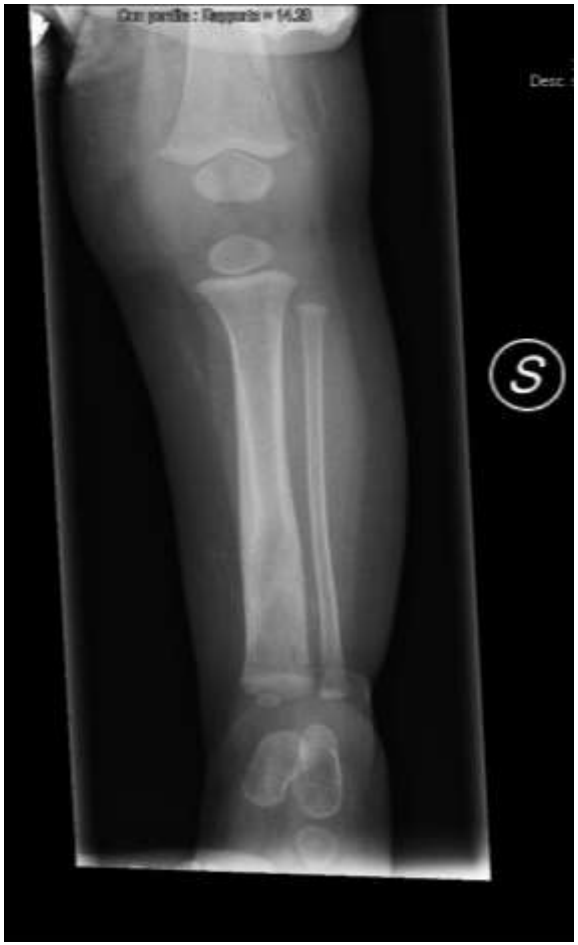


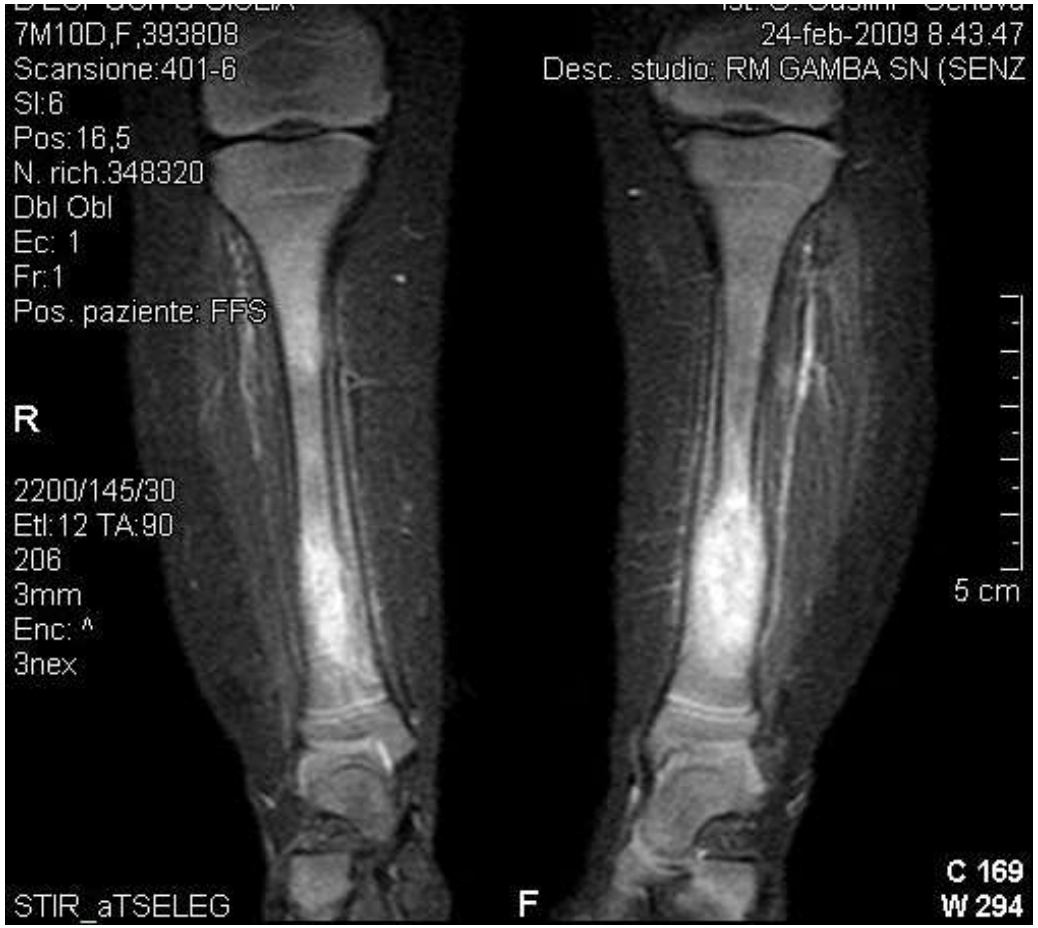


Disciitis



Congenital syphilis





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Viral arthritis

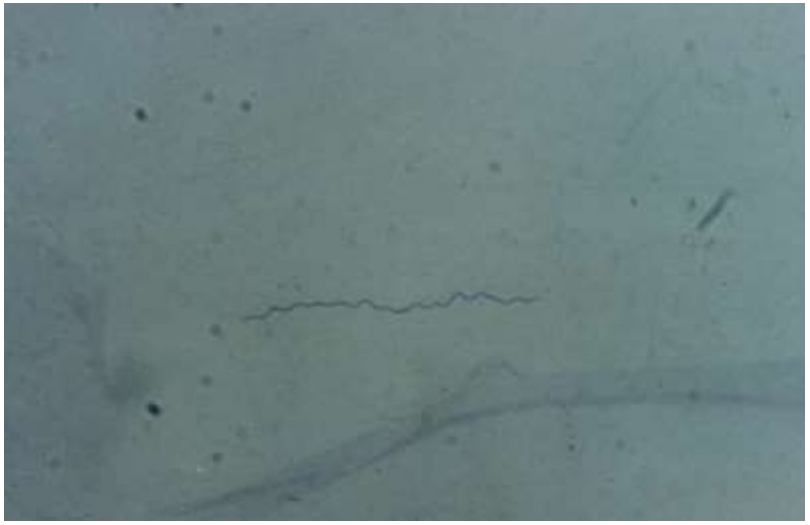
- Measles
- Rubella
- Varicella
- Parvovirus B19
- Epstein-Barr virus
- Herpesvirus
- Adenovirus
- Hepatitis B virus
- Coxsakie
- Mumps

Reactive arthritis

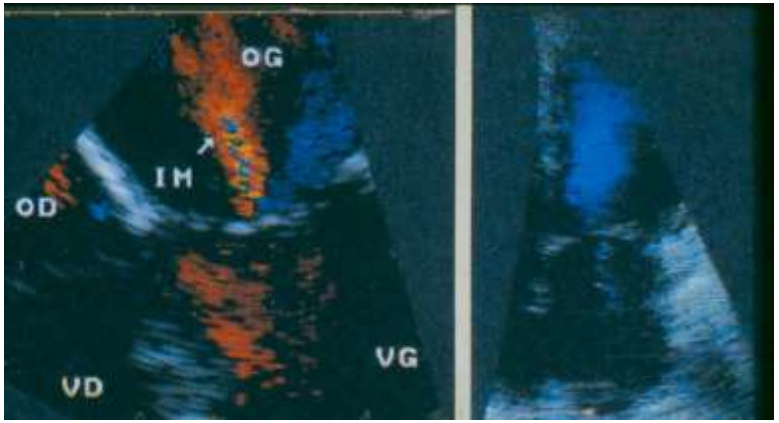
- Yersinia, Shigella, Salmonella, Chlamydia infections
- HLA-B27 +

- Oligoarthritis (*post-dissenteric arthritis*) or the (rare) triad of arthritis, conjunctivitis and urethritis (*Reiter syndrome)*

Lyme disease



Rheumatic fever



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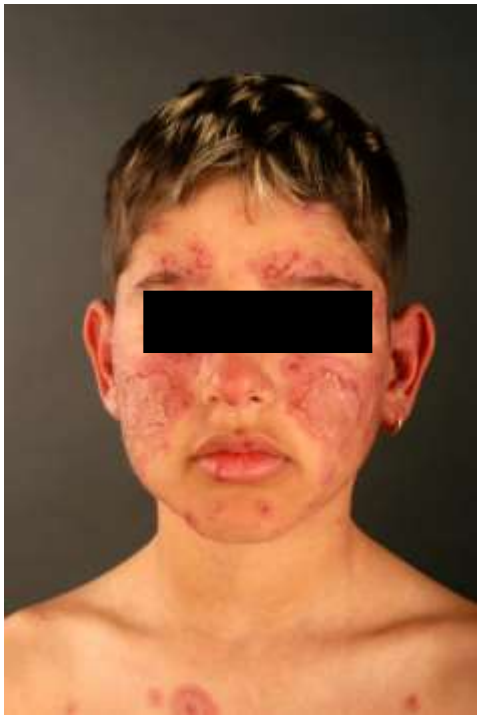
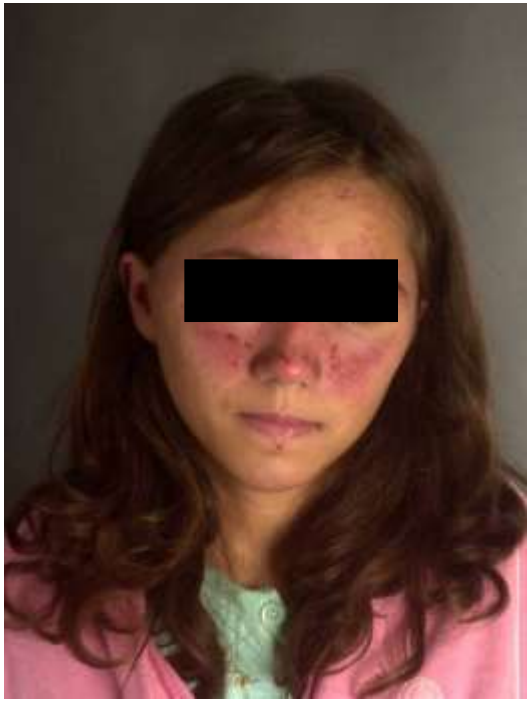
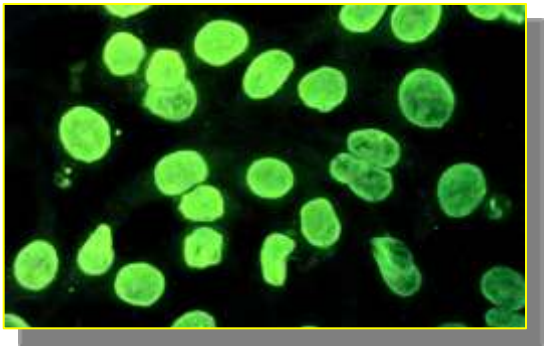
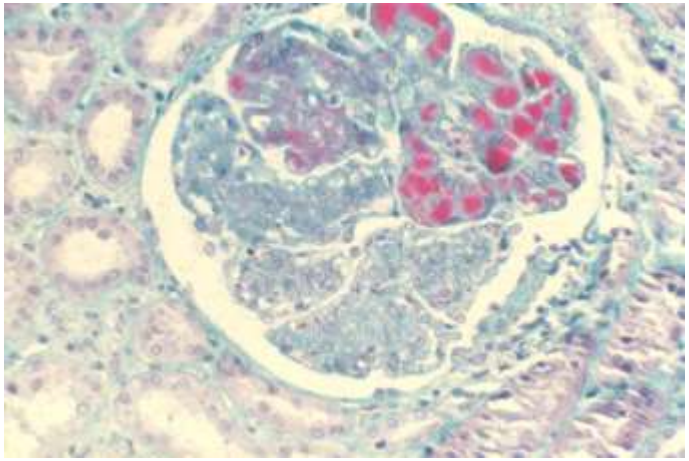
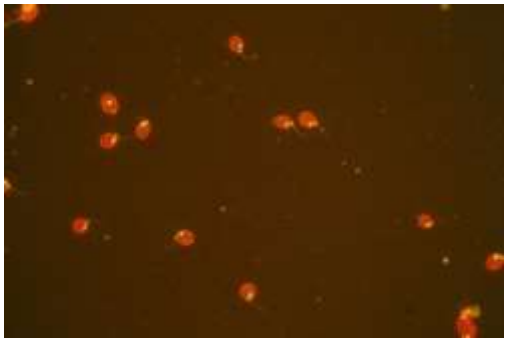
SLE



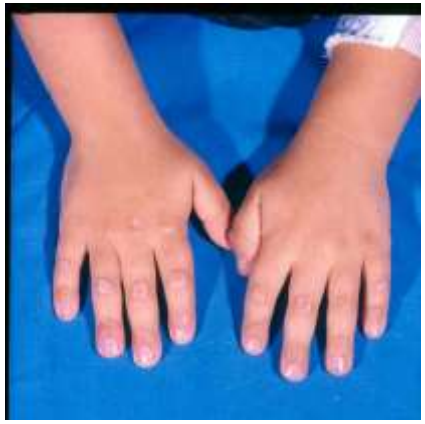


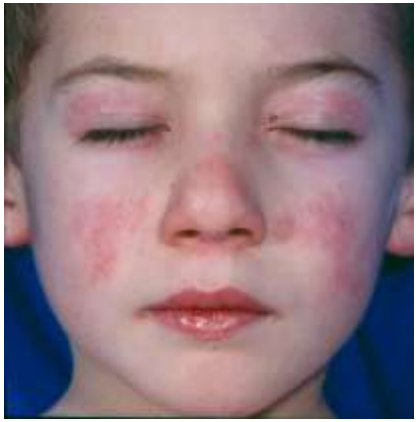


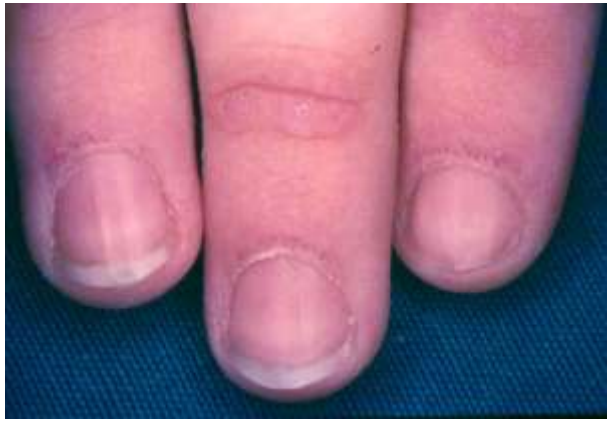


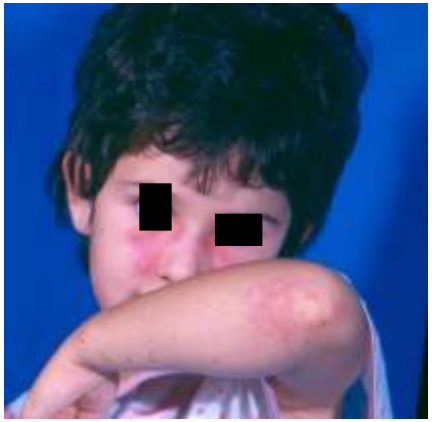


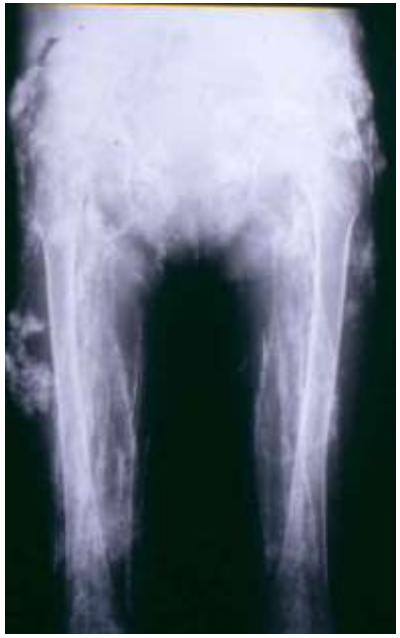
Dermatomyositis

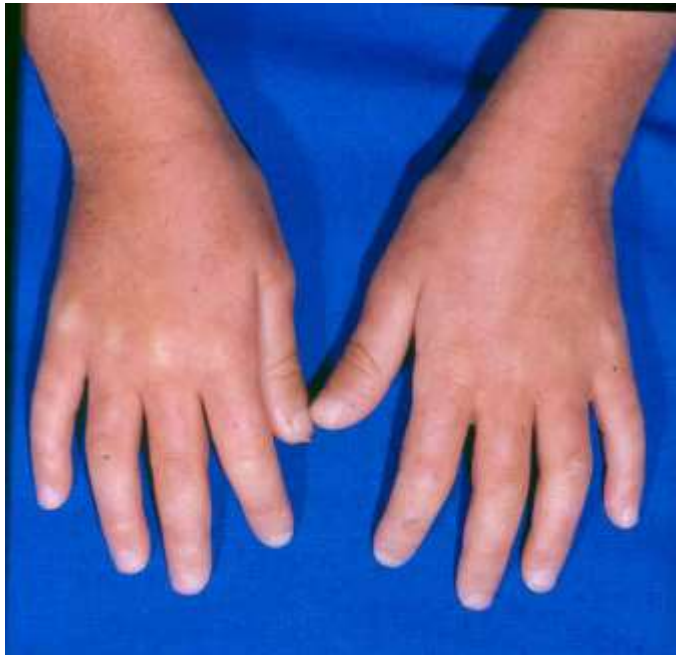


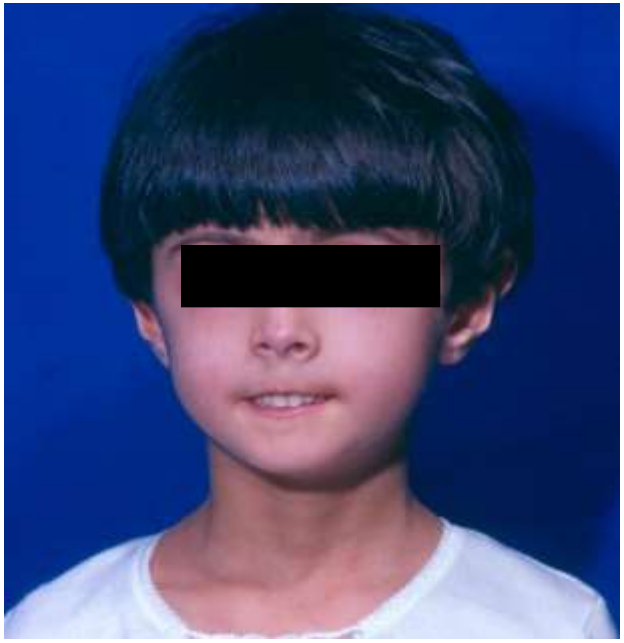








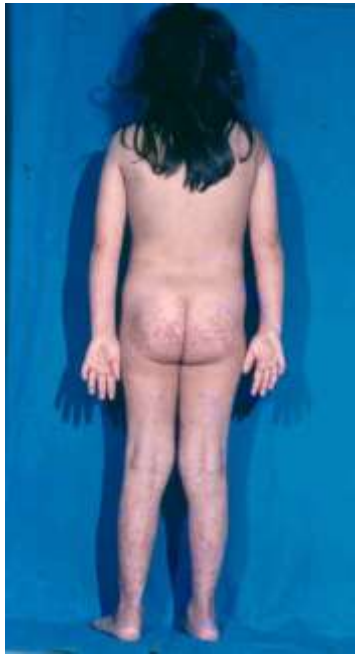


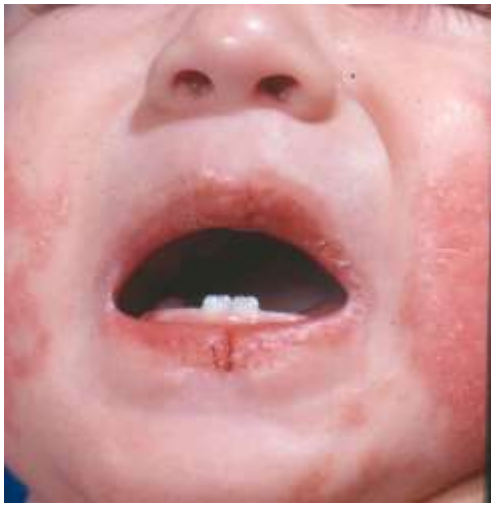


Systemic

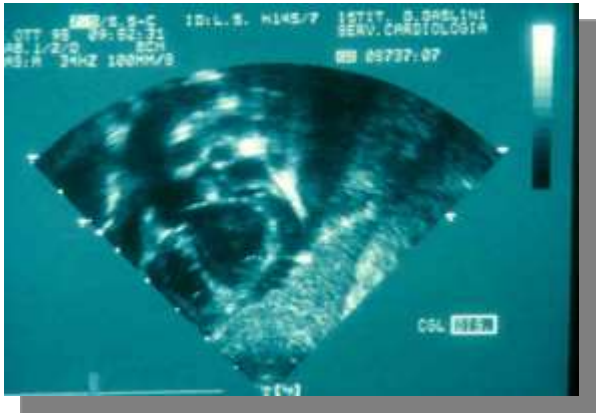
scleroderma

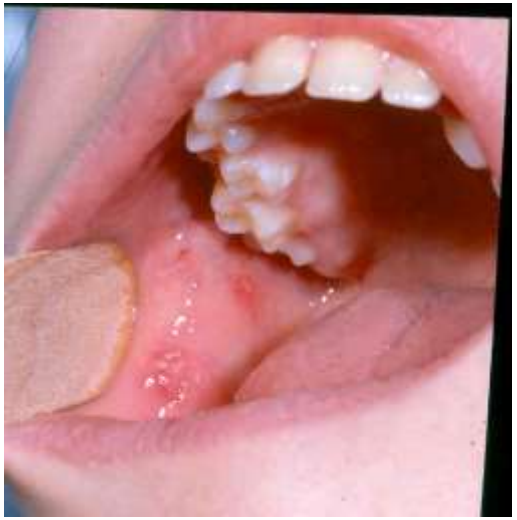
Henoch-Schoenlein synd.



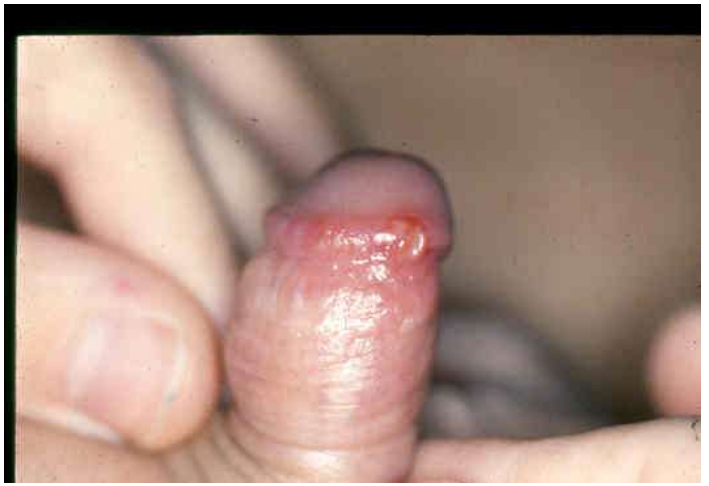


Kawasaki disease

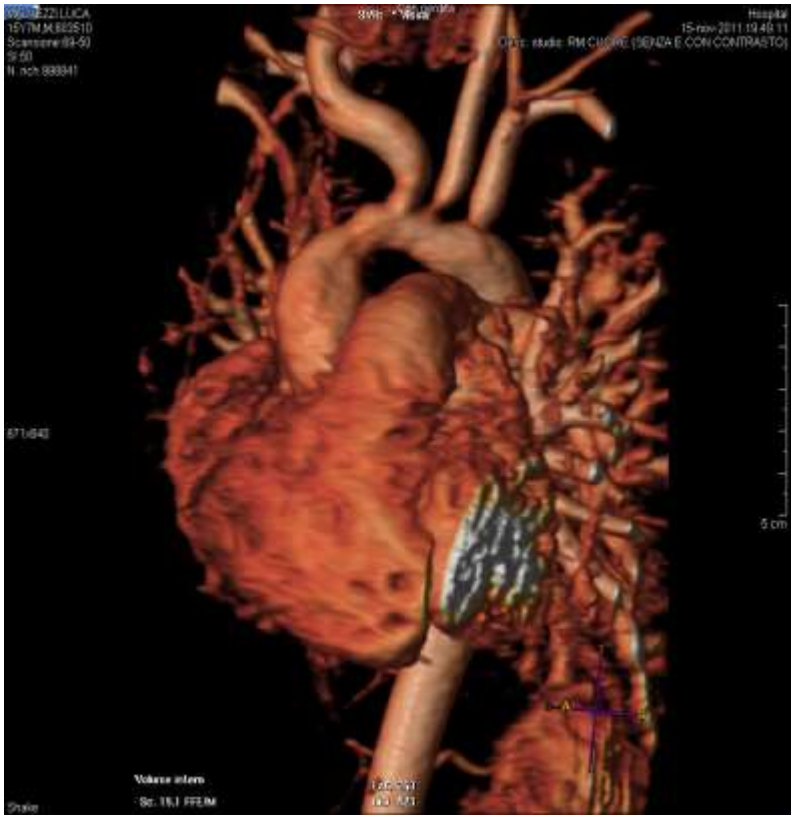


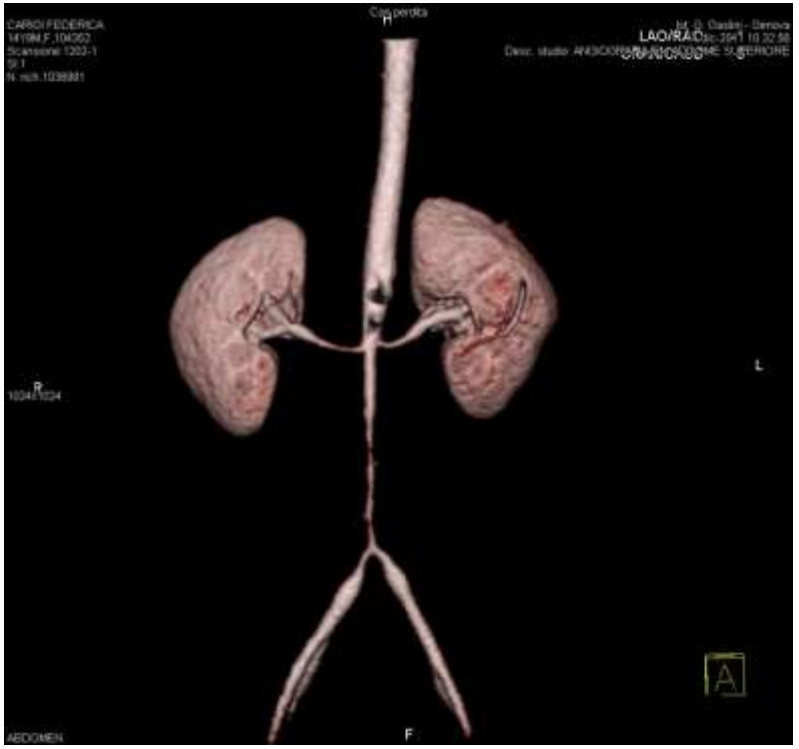


Behcet syndrome

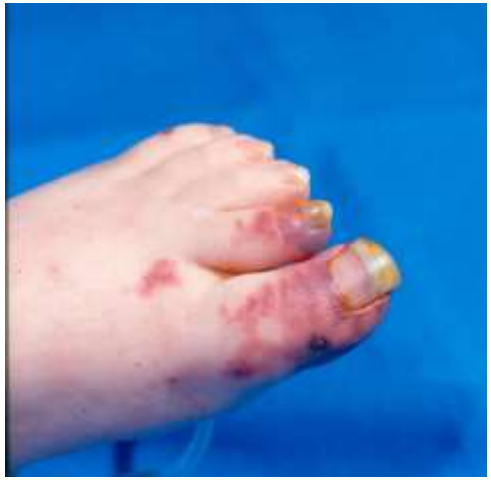


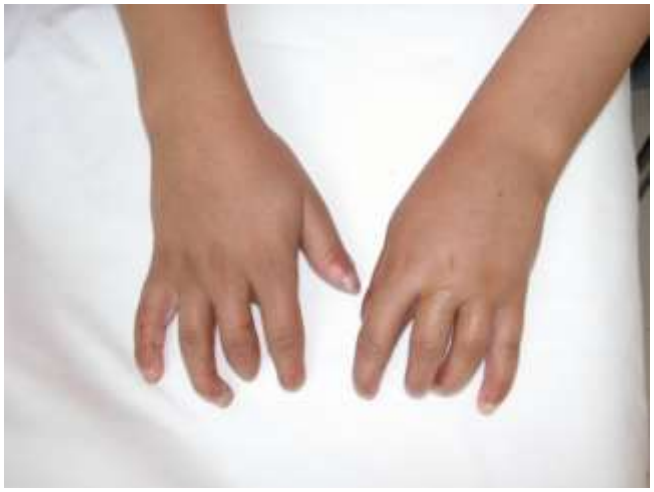
Takayasu arteritis

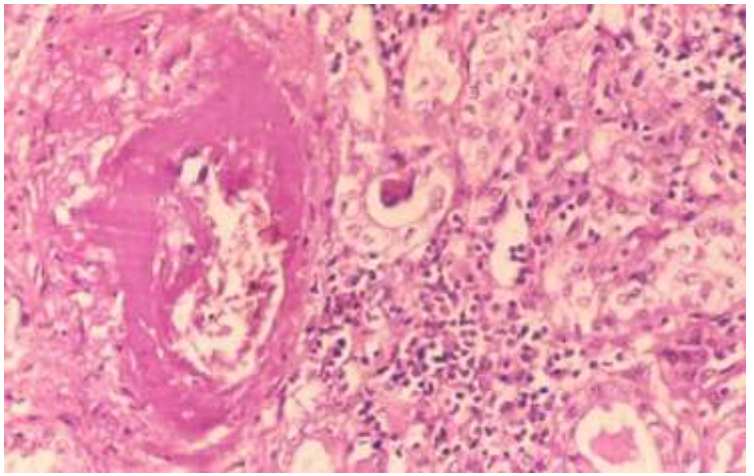




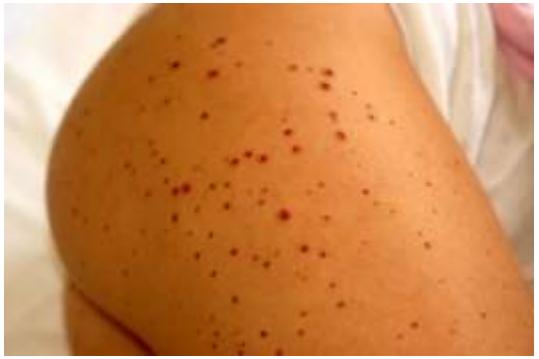
Polyarteritis nodosa

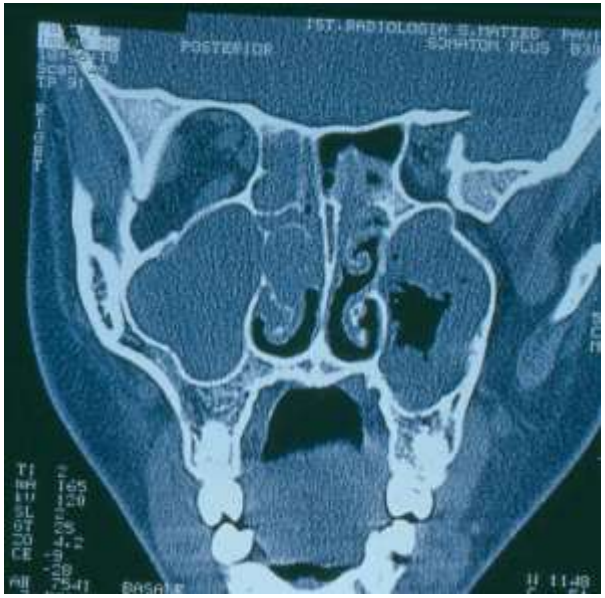


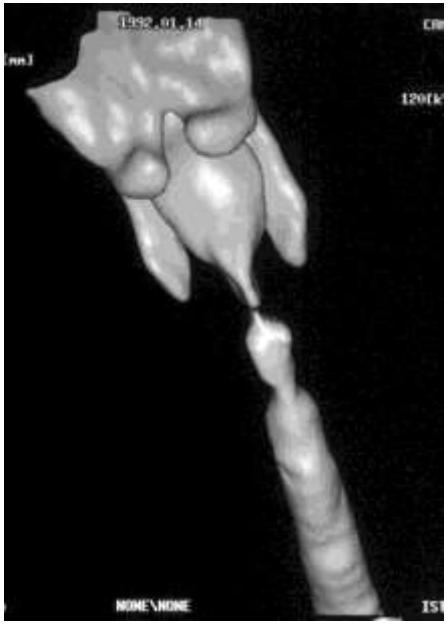


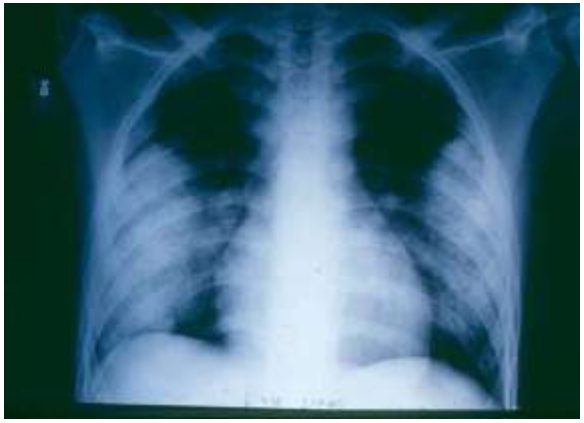


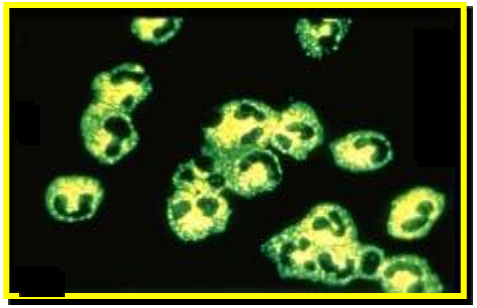
Wegener's granulomatosis



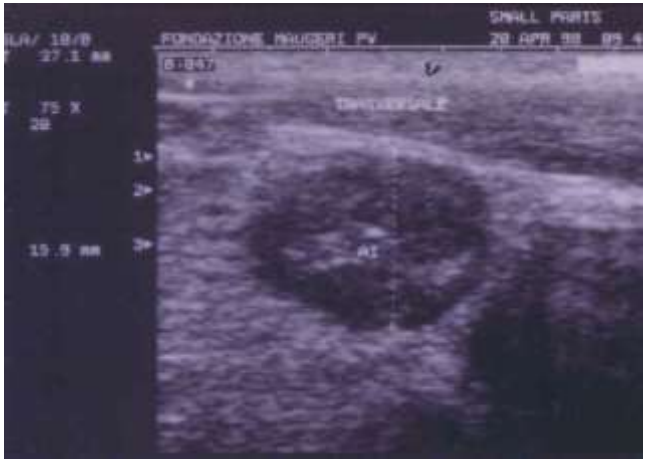


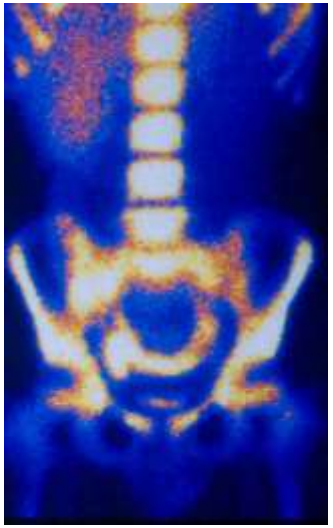




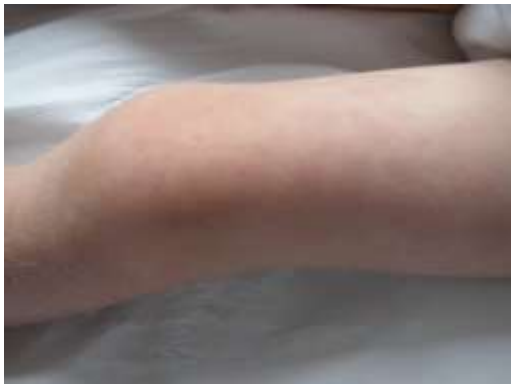


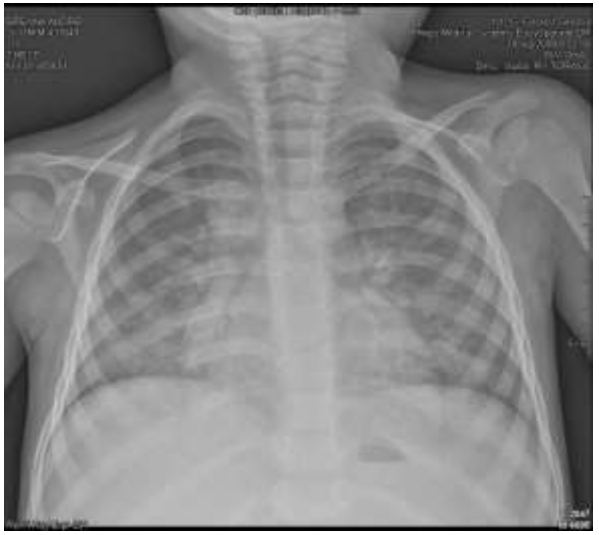
Crohn’s disease





Sarcoidosis





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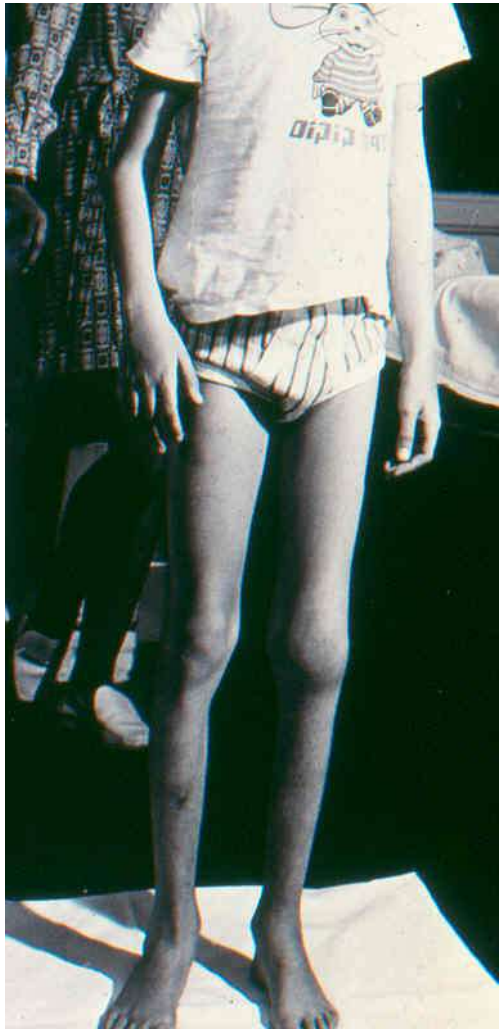
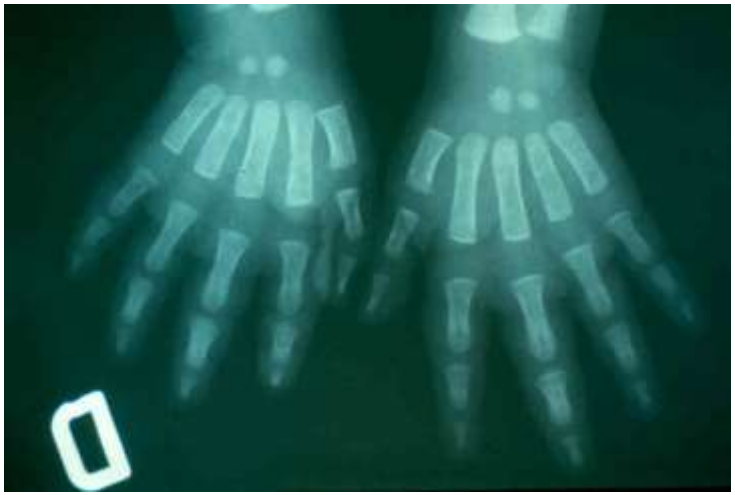
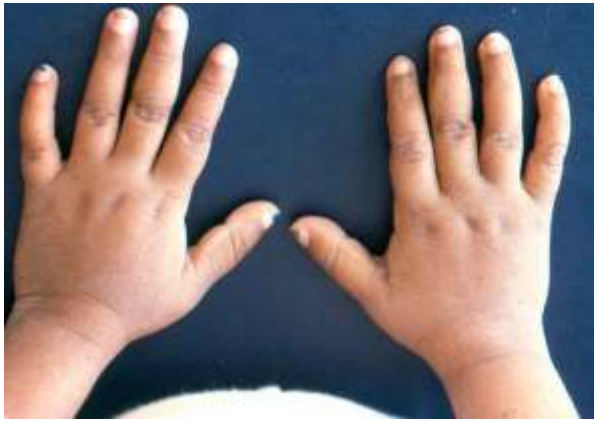
Hemophilia



Drepanocytosis





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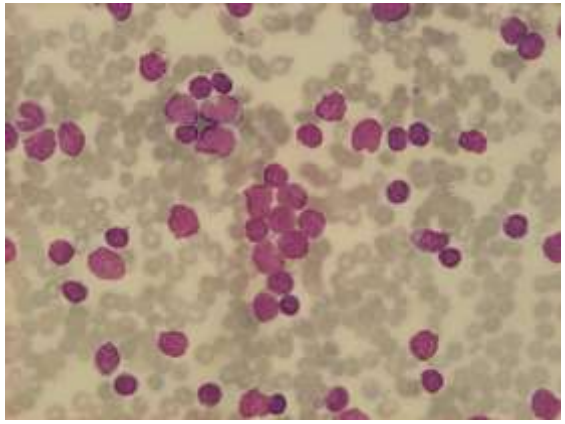
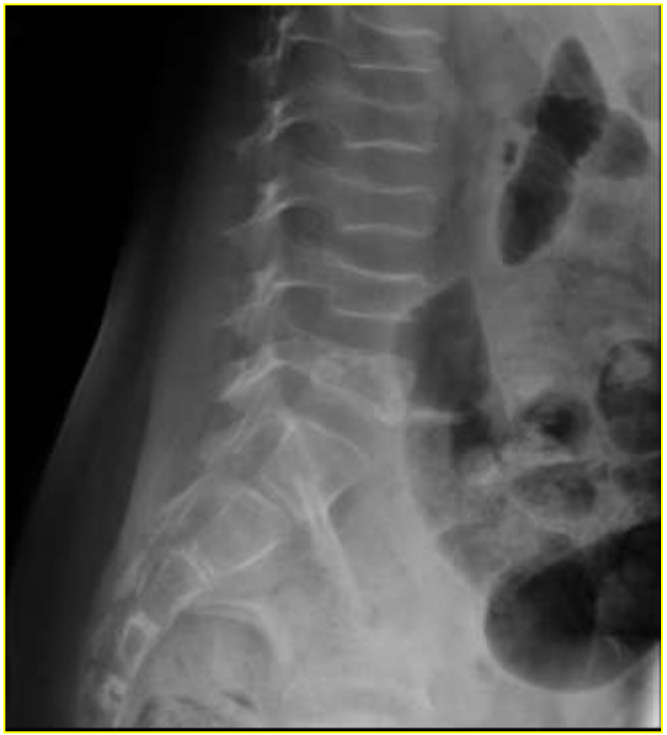
Leukemia



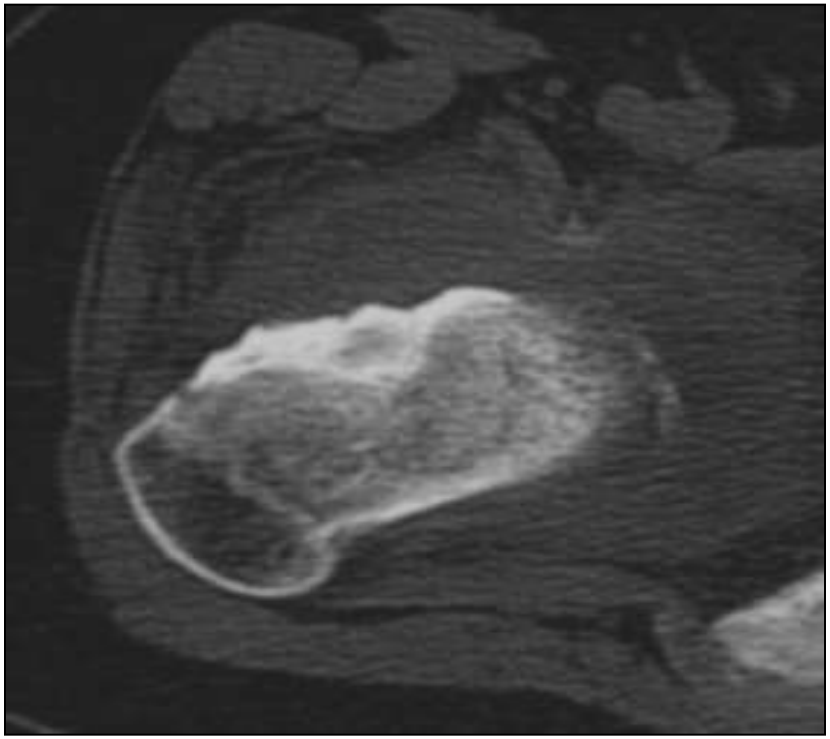
Limphoma

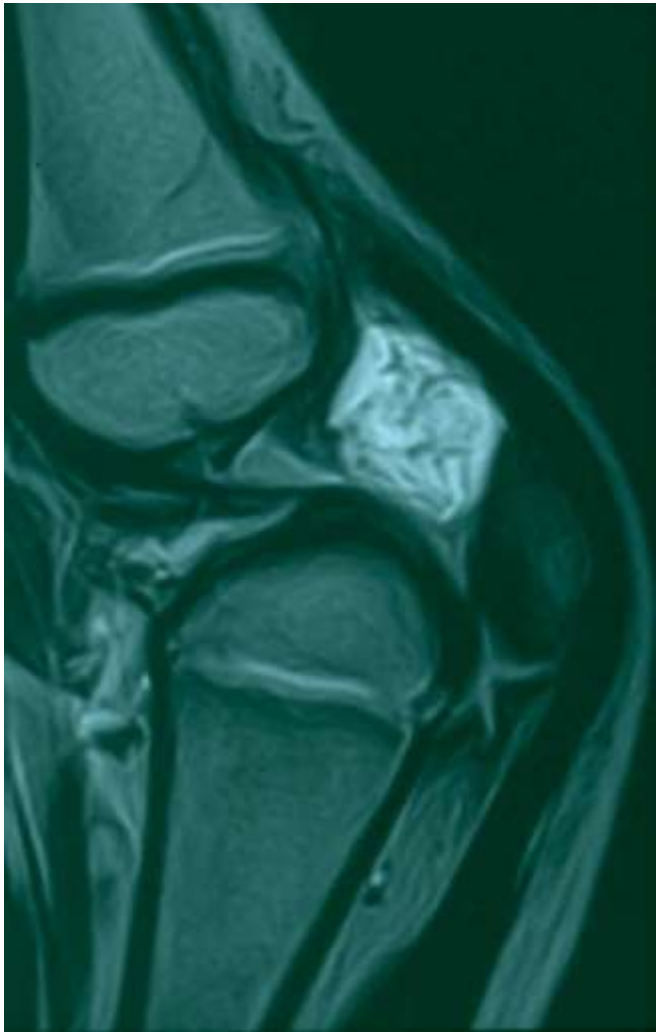


Neuroblastoma

Hemangioma

Osteoid osteoma





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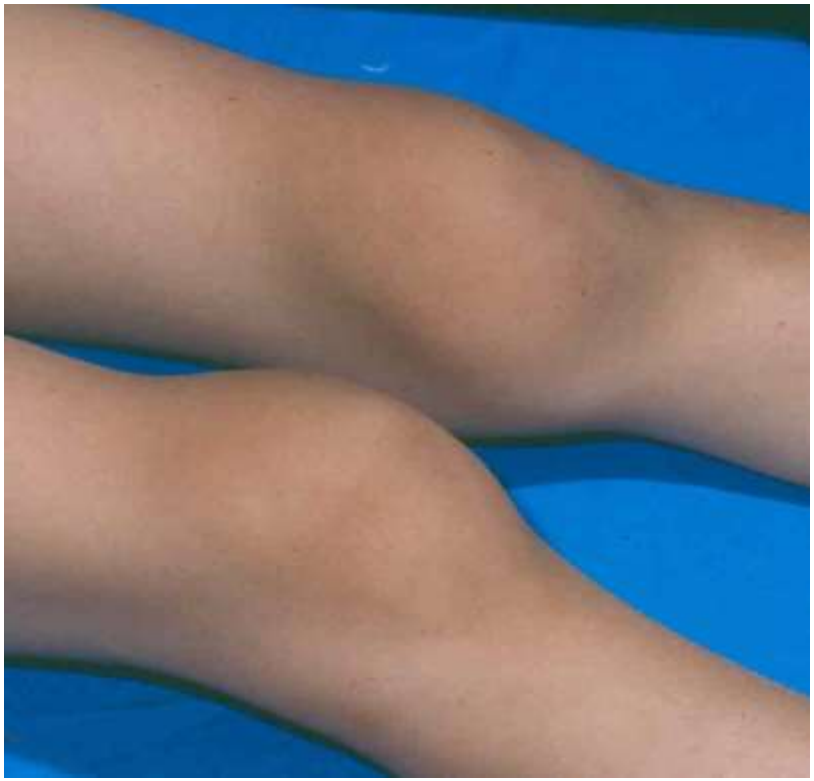
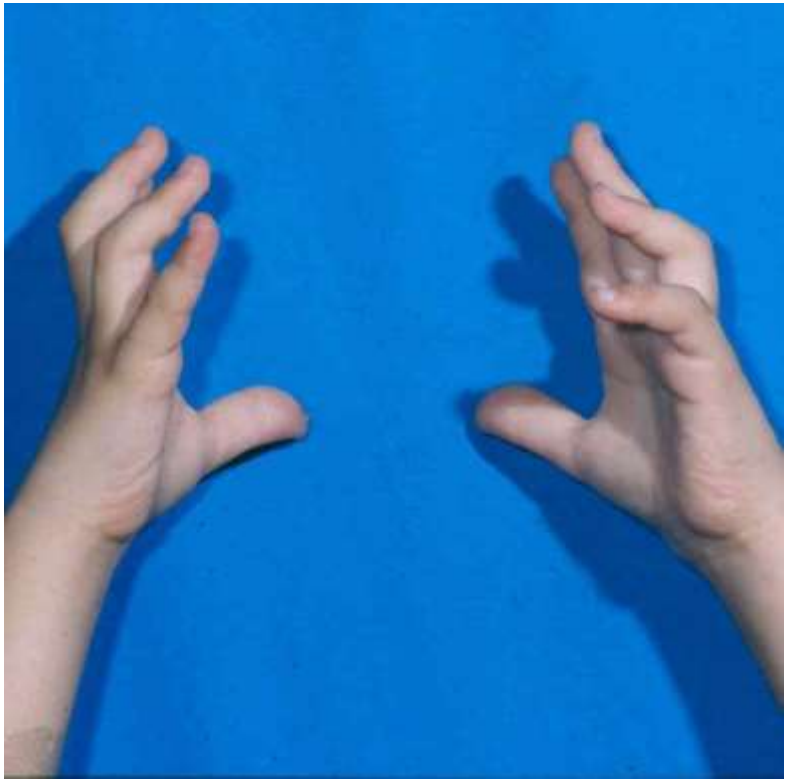
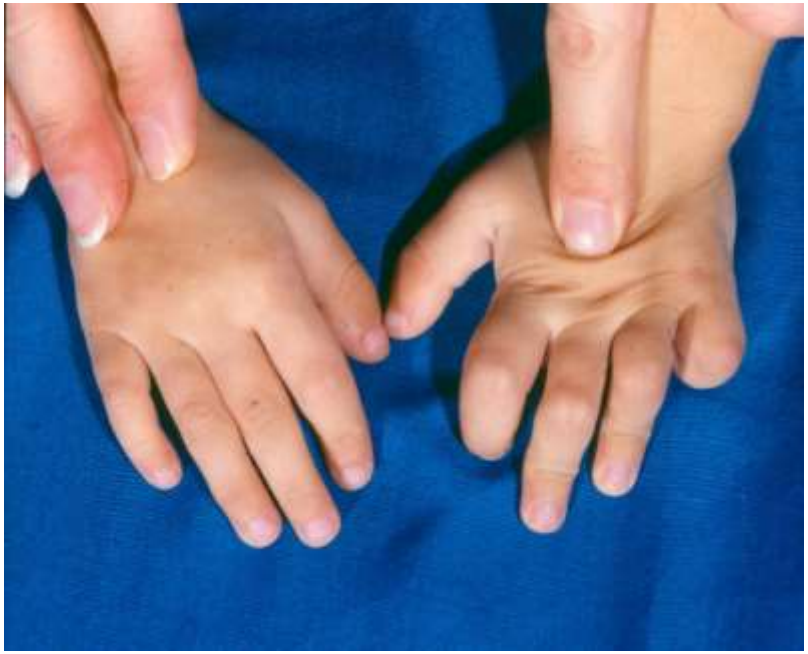
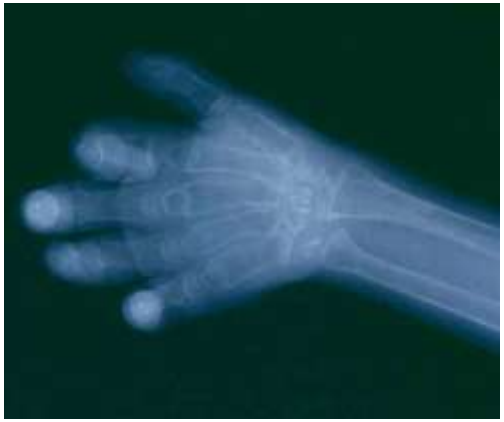
Camptodactyly-arthritis syndrome

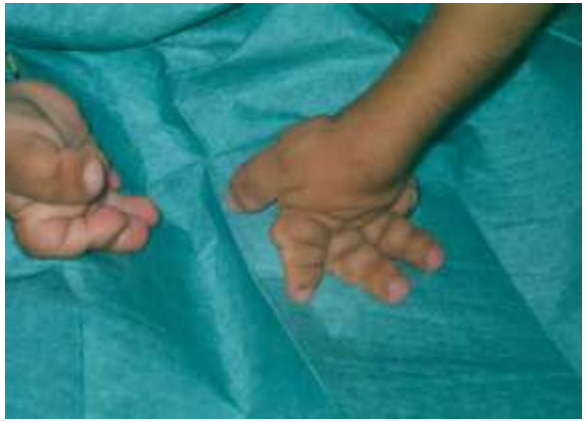




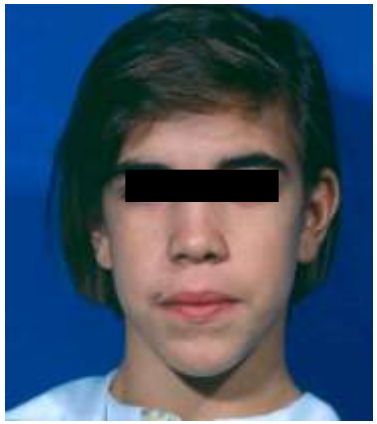
Carpo-tarsal osteolysis



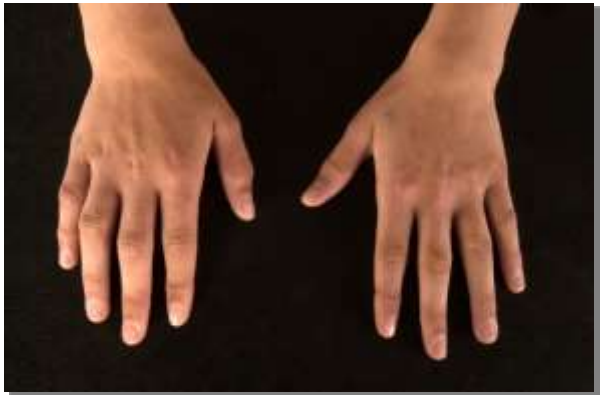


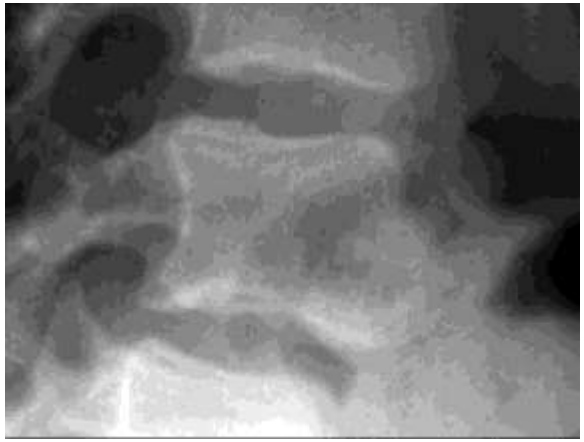


Mucopolysaccharidosis

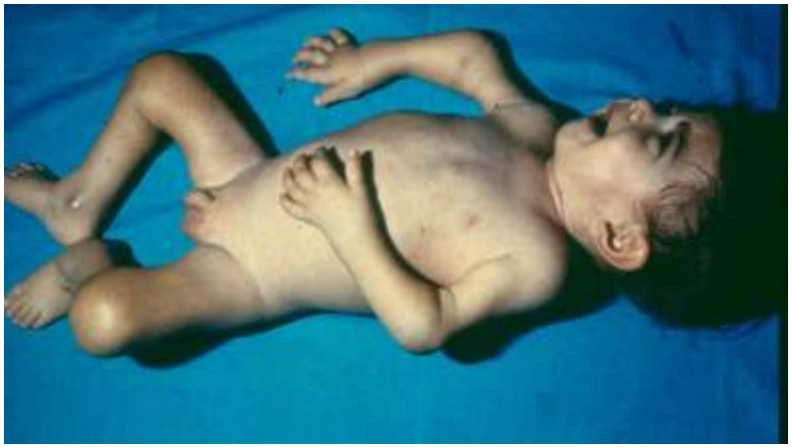


Mucolipidosis

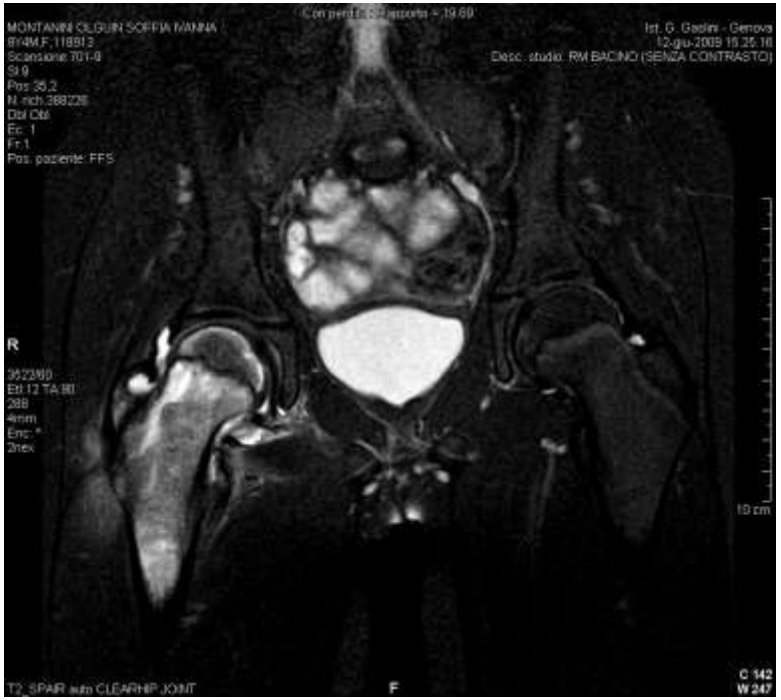




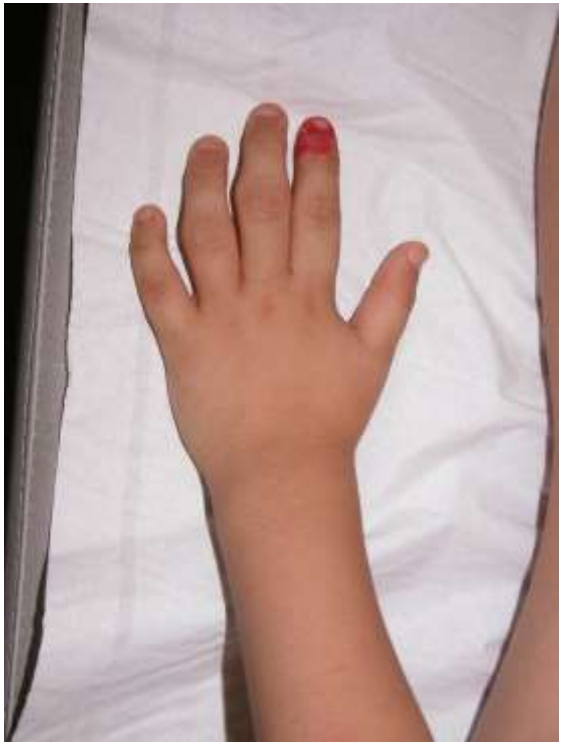
Farber’s disease

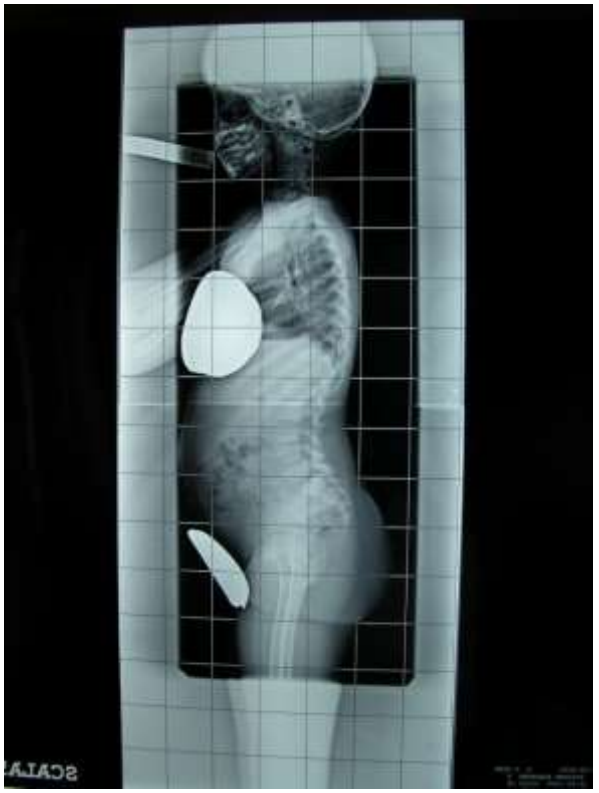


Gaucher’s disease



Progressive pseudorheumatoid chondrodysplasia





Autoinflammatory diseases

- Inherited diseases
- Onset often in pediatric age
- Recurrent bouts of seemingly unprovoked inflammation characterized by fever +/-:
    - serositis
    - synovitis
    - rash
- Recurrent or persistent inflammation with specific organ involvement

Cryopyrin associated periodic syndrome (CAPS): spectrum of disease

Familial cold autoinflammatory syndrome (FCAS)

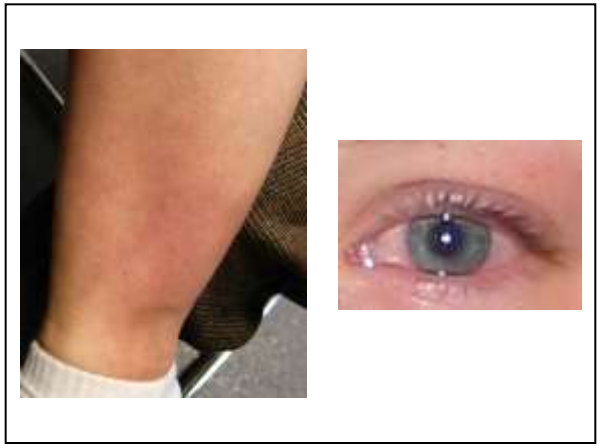
- Autosomal dominant
- Cold-induced
  - Rash
  - Arthralgia
  - Conjunctivitis

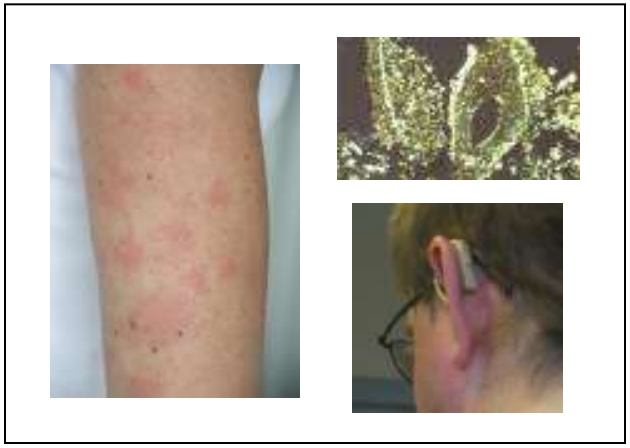
Muckle–Wells syndrome (MWS)

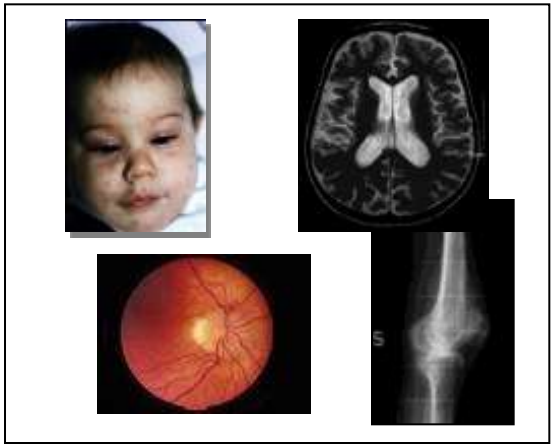
- Autosomal dominant
- Urticarial rash
- Sensorineural deafness
- AA amyloidosis (in 25% of patients) leading to renal failure

NOMID/CINCA

- Sporadic
- Progressive chronic meningitis
- Deafness
- Visual and intellectual damage
- Destructive arthritis







MILD

SEVERE

NOMID/CINCA, neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous and articular syndrome

PAPA syndrome

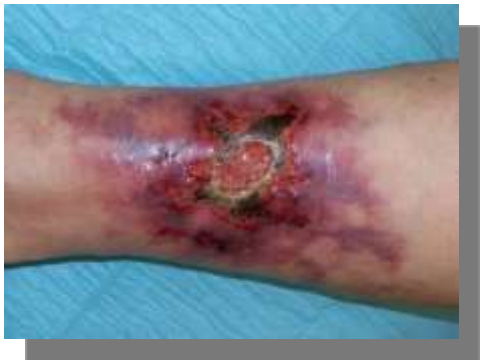
pyogenic arthritis

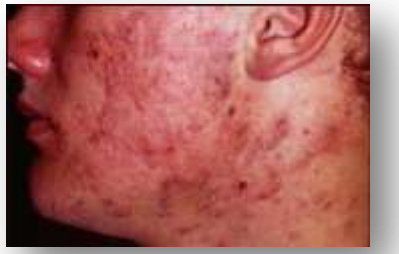
acne

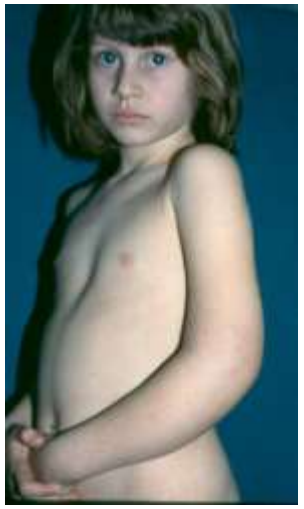
pyoderma gangrenosum

PSTPIP1/CD2BP1 mutations (interacts with pyrin)

Autosomal dominant





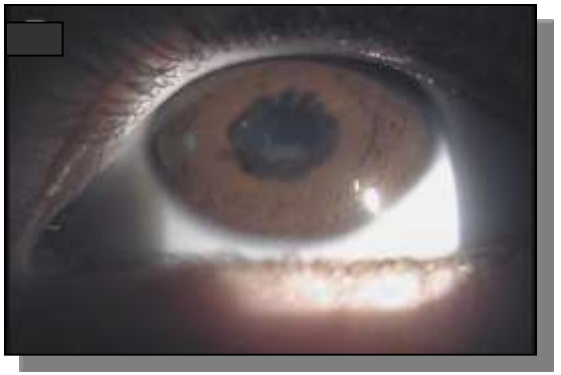


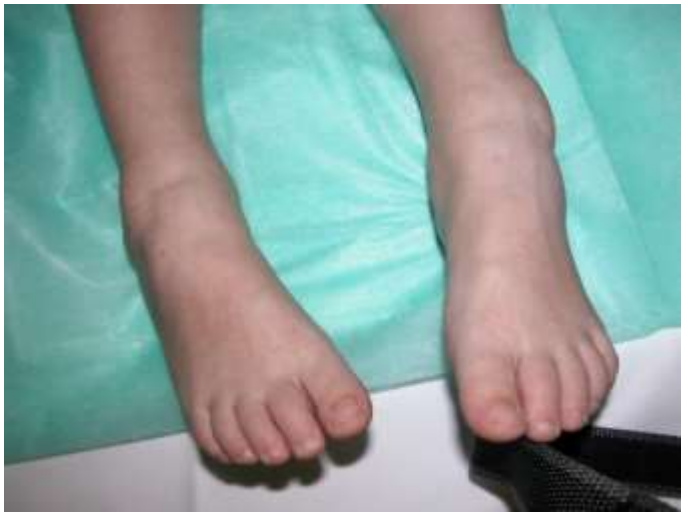
Blau syndrome

granulomatous polyarthritis

panuveitis

exanthema





mutations of NOD2 (intracellular sensor of bacteria)

Autosomal dominant

ORIGINAL ARTICLE

Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2

Q. Zhou, D. Yang, A.K. Ombrello, Andrey V. Zavialov, C. Toro, Anton V. Zavialov, D.L. Stone, J.J. Chae, S.D. Rosenzweig, K. Bishop, K.S. Barron, H.S. Kuehn, P. Hoffmann, A. Negro, W.L. Tsai, E.W. Cowen, W. Pei, J.D. Milner, C. Silvin, T. Heller, D.T. Chin, N.J. Patronas, J.S. Barber, C.-C.R. Lee, G.M. Wood, A. Ling, S.J. Kelly, D.E. Kleiner, J.C. Mullikin, N.J. Ganson, H.H. Kong, S. Hambleton, F. Candotti, M.M. Quezado, K.R. Calvo, H. Alao, B.K. Barham, A. Jones, J.F. Meschia, B.B. Worrall, S.E. Kasner, S.S. Rich, R. Goldbach-Mansky, M. Abinun, E. Chalom, A.C. Gotte, M. Punaro, V. Pascual, J.W. Verbsky, T.R. Torgerson, N.G. Singer, T.R. Gershon, S. Ozen, O. Karadag, T.A. Fleisher, E.F. Remmers, S.M. Burgess, S.L. Moir, M. Gadina, R. Sood, M.S. Hershfield, M. Boehm, D.L. Kastner, and I. Aksentijevich

N Engl J Med 2014;370:911-20.

9 patients

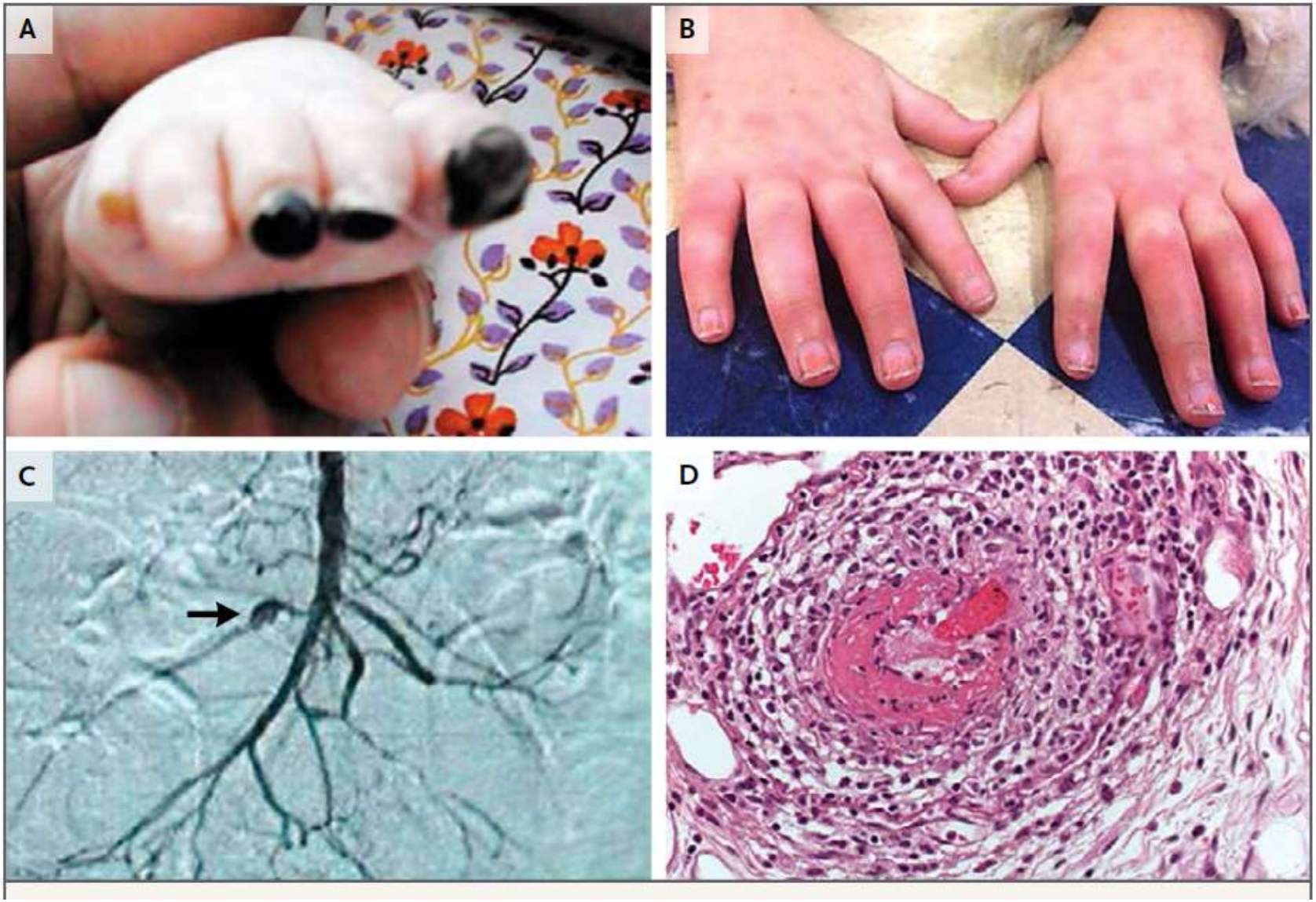
ORIGINAL ARTICLE

Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Paulina Navon Elkan, M.D., Sarah B. Pierce, Ph.D., Reeval Segel, M.D., Tom Walsh, Ph.D., Judith Barash, M.D., Shai Padeh, M.D., Abraham Zlotogorski, M.D., Yackov Berkun, M.D., Joseph J. Press, M.D., Masha Mukamel, M.D., Isabel Voth, M.D., Philip J. Hashkes, M.D., Liora Harel, M.D., Vered Hoffer, M.D., Eduard Ling, M.D., Ph.D., Fatos Yalcinkaya, M.D., Ozgur Kasapcopur, M.D., Ming K. Lee, Ph.D., Rachel E. Klevit, D.Phil., Paul Renbaum, Ph.D., Ariella Weinberg-Shukron, B.Sc.Med., Elif F. Sener, Ph.D., Barbara Schormair, Ph.D., Sharon Zeligson, M.Sc., Dina Marek-Yagel, Ph.D., Tim M. Strom, M.D., Mordechai Shohat, M.D., Amihood Singer, M.D., Alan Rubinow, M.D., Elon Pras, M.D., Juliane Winkelmann, M.D., Mustafa Tekin, M.D., Yair Anikster, M.D., Ph.D., Mary-Claire King, Ph.D., and Ephrat Levy-Lahad, M.D.

N Engl J Med 2014;370:921-31.

24 Patients (50% fulfilling the diagnostic criteria for PAN)



Navon Elkan P et al NEJM 2014

Most common clinical features

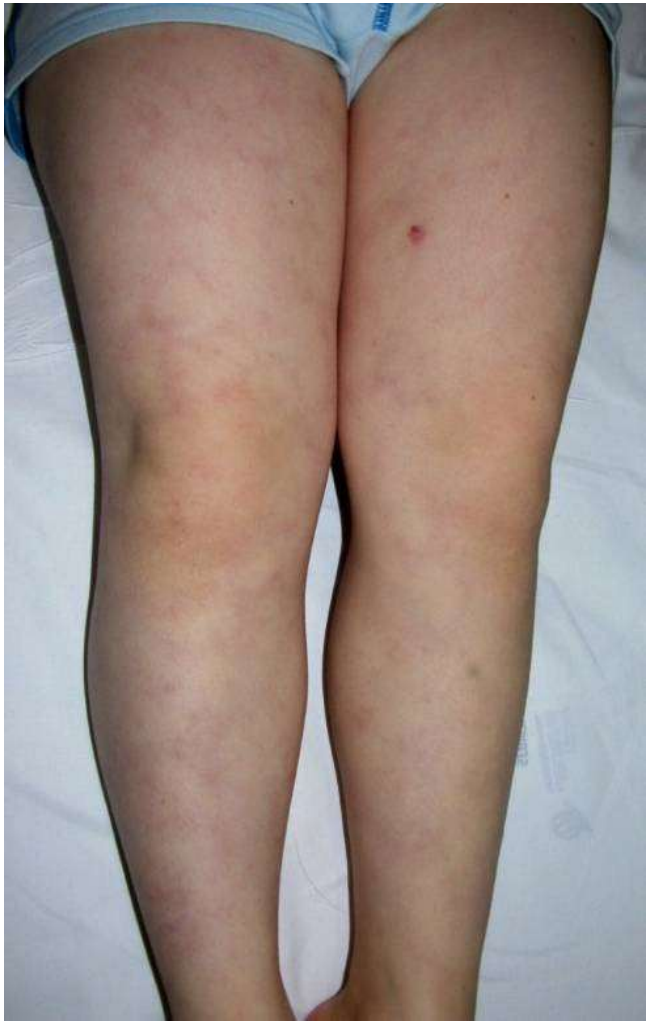
- Recurrent fevers
- Livedo reticularis
- Early-onset, recurrent hemorragic strokes
- High ESR and CRP
- Pathological findings consistent with PAN

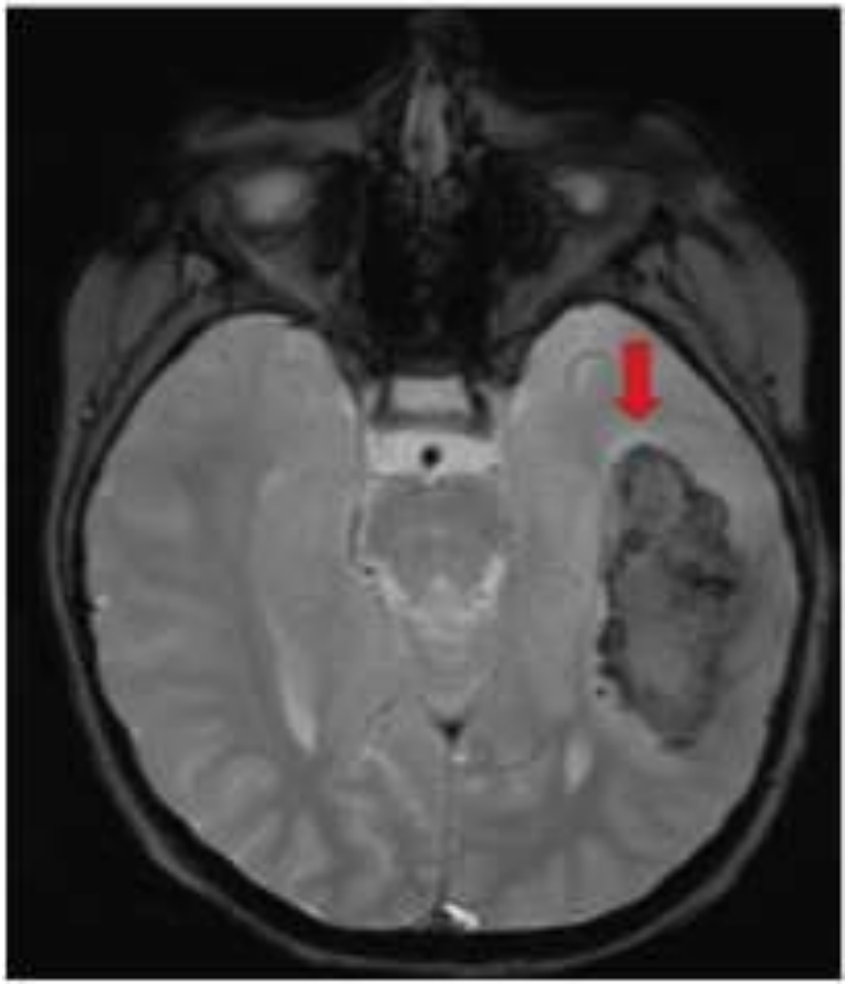
- Impressive efficacy of anti-TNF treatment

Clinical features

- Mutation common among persons of Georgian Jewish ancestry where mild cases were often recognized in patients only after severe disease developed in a relative
- Clinical manifestations range from early-onset multiple strokes to limited cutaneous lesions in advanced adult age
- Mutations in the ADA2 gene may be more common than expected and may be associated with a larger spectrum of disorders. This suggests that in the coming years the field of vasculits could be revolutionized by genetic studies.

Navon Elkan et al NEJM 2014



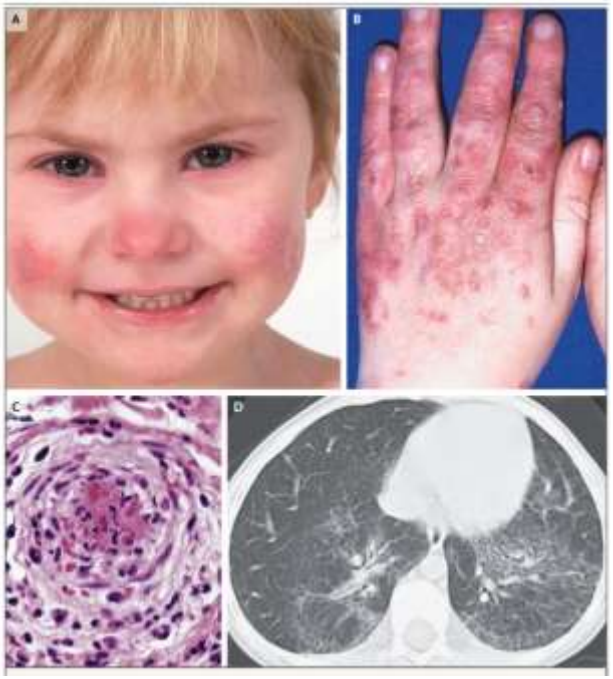


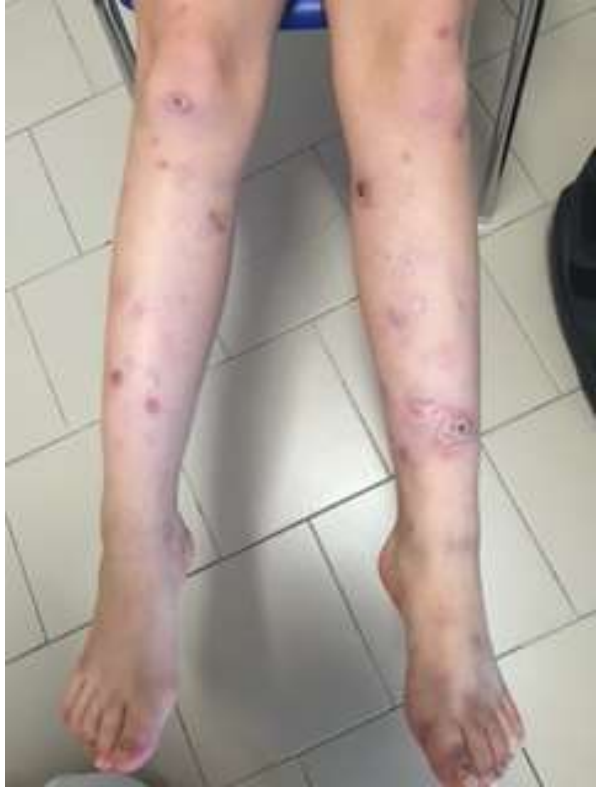
ORIGINAL ARTICLE

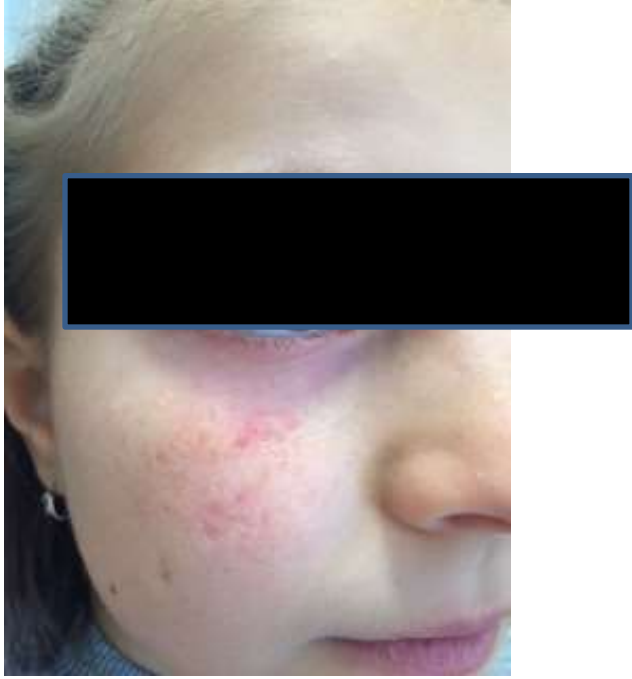
Activated STING in a Vascular and Pulmonary Syndrome

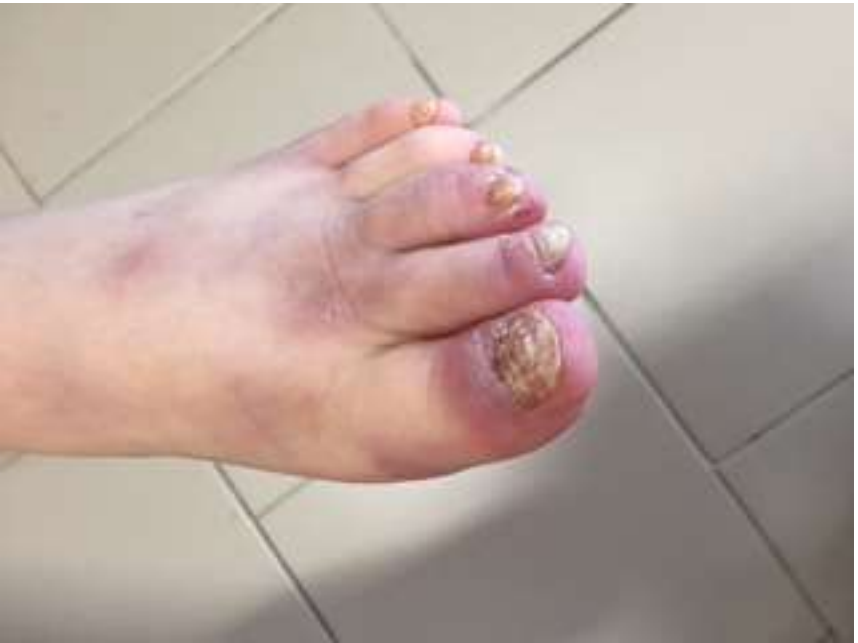
Y. Liu, A.A. Jesus, B. Marrero, D. Yang, S.E. Ramsey, G.A. Montealegre Sanchez, K. Tenbrock, H. Wittkowski, O.Y. Jones, H.S. Kuehn, C.-C.R. Lee, M.A. DiMattia, E.W. Cowen, B. Gonzalez, I. Palmer, J.J. DiGiovanna, A. Biancotto, H. Kim, W.L. Tsai, A.M. Trier, Y. Huang, D.L. Stone, S. Hill, H.J. Kim, C. St. Hilaire, S. Gurprasad, N. Plass, D. Chapelle, I. Horkayne-Szakaly, D. Foell, A. Barysenka, F. Candotti, S.M. Holland, J.D. Hughes, H. Mehmet, A.C. Issekutz, M. Raffeld, J. McElwee, J.R. Fontana, C.P. Minniti, S. Moir, D.L. Kastner, M. Gadina, A.C. Steven, P.T. Wingfield, S.R. Brooks, S.D. Rosenzweig, T.A. Fleisher, Z. Deng, M. Boehm, A.S. Paller, and R. Goldbach-Mansky

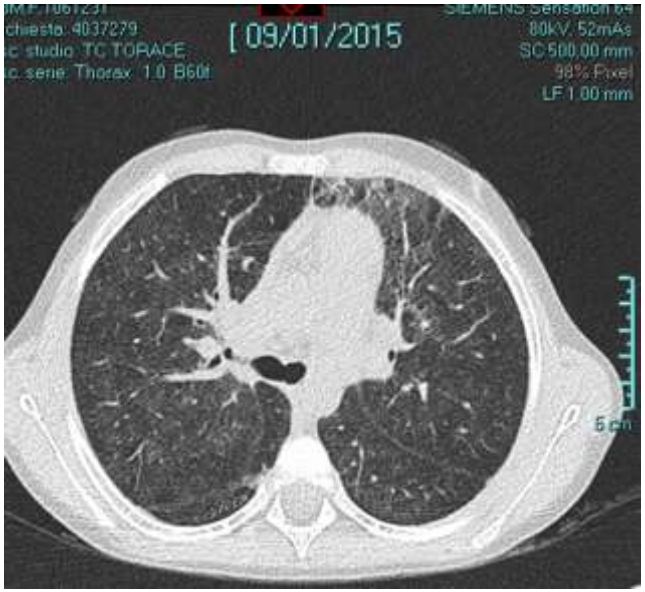
N Engl J Med. 2014;371:507-18

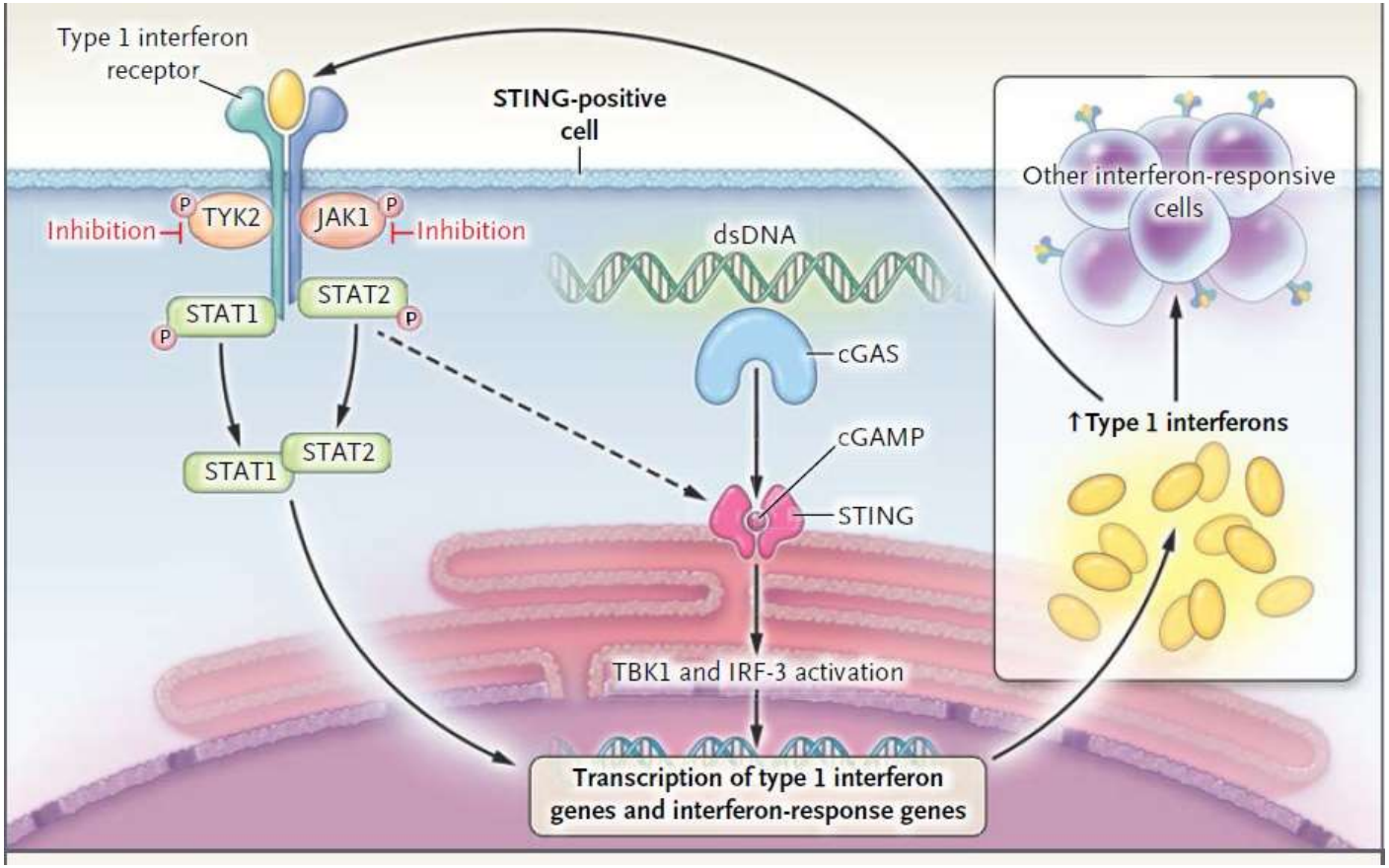

A
B
C
D








[09/01/2015
80kV, 52mAs
SC 500,00 mm
98% Pixel
LF 1,00 mm
5 cm



In patients with SAVI, constitutively activated STING leads to increased transcription of the type 1 interferon gene, IFNB1, which encodes interferon-β.

Liu et al NEJM 2014

Association of a Mutation in *LACC1* With a Monogenic Form of Systemic Juvenile Idiopathic Arthritis

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 1, January 2015, pp 288–295

Salma M. Wakil,[1] Dorota M. Monies,[1] Mohamed Abouelhoda,[1] Nada Al-Tassan,[1] Haya Al-Dusery,[2] Ewa A. Naim,[1] Banan Al-Younes,[1] Jameela Shinwari,[2] Futwan A. Al-Mohanna,[2] Brian F. Meyer,[1] and Sulaiman Al-Mayouf[2]

COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis

Levi B Watkin[1,2,16], Birthe Jessen[3,16], Wojciech Wiszniewski[4,16], Timothy J Vece[1], Max Jan[3], Youbao Sha[5], Maike Thamsen[3], Regie L P Santos-Cortez[6], Kwanghyuk Lee[6], Tomasz Gambin[4], Lisa R Forbes[1,2], Christopher S Law[3], Asbjørg Stray-Pedersen[2,4], Mickie H Cheng[3], Emily M Mace[1,2], Mark S Anderson[3], Dongfang Liu[1,2], Ling Fung Tang[7], Sarah K Nicholas[1,2], Karen Nahmod[1,2], George Makedonas[1,2], Debra L Canter[1,2], Pui-Yan Kwok[7,8], John Hicks[9], Kirk D Jones[10], Samantha Penney[4], Shalini N Jhangiani[11], Michael D Rosenblum[8], Sharon D Dell[12], Michael R Waterfield[13], Feroz R Papa[3], Donna M Muzny[11], Noah Zaitlen[3], Suzanne M Leal[6], Claudia Gonzaga-Jauregui[4], Baylor-Hopkins Center for Mendelian Genomics[14], Eric Boerwinkle[11,15], N Tony Eissa[5], Richard A Gibbs[4,11], James R Lupski[1,4,11,17], Jordan S Orange[1,2,17] & Anthony K Shum[3,7,17]

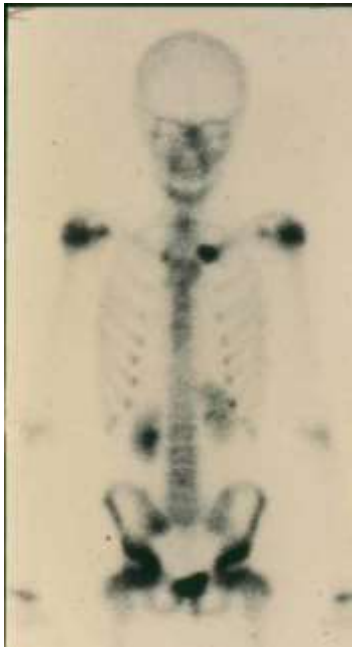
Nature Genetics June 2015

Loss-of-function mutations in *TNFAIP3* leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease

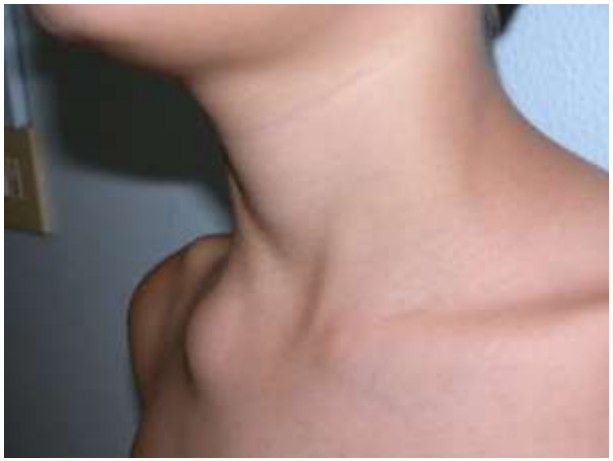
Qing Zhou[1,19], Hongying Wang[1,19], Daniella M Schwartz[2], Monique Stoffels[1], Yong Hwan Park[1], Yuan Zhang[3], Dan Yang[4], Erkan Demirkaya[5], Masaki Takeuchi[1], Wanxia Li Tsai[6], Jonathan J Lyons[3], Xiaomin Yu[3], Claudia Ouyang[7], Celeste Chen[1], David T Chin[1], Kristien Zaal[8], Settara C Chandrasekharappa[9], Eric P Hanson[7], Zhen Yu[4], James C Mullikin[10], Sarfaraz A Hasni[11], Ingrid E Wertz[12], Amanda K Ombrello[1], Deborah L Stone[1], Patrycja Hoffmann[1], Anne Jones[1], Beverly K Barham[1], Helen L Leavis[13], Annet van Royen-Kerkof[14], Cailin Sibley[15], Ezgi D Batu[16], Ahmet Gül[17], Richard M Siegel[7], Manfred Boehm[4], Joshua D Milner[3], Seza Ozen[16], Massimo Gadina[6], JaeJin Chae[1], Ronald M Laxer[18], Daniel L Kastner[1,20] & Ivona Aksentijevich[1,20]

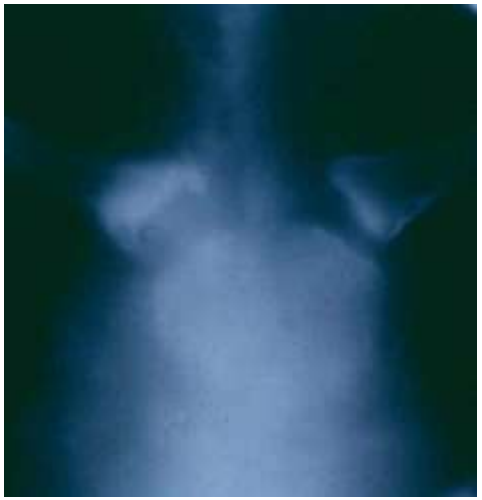
Nature Genetics January 2016

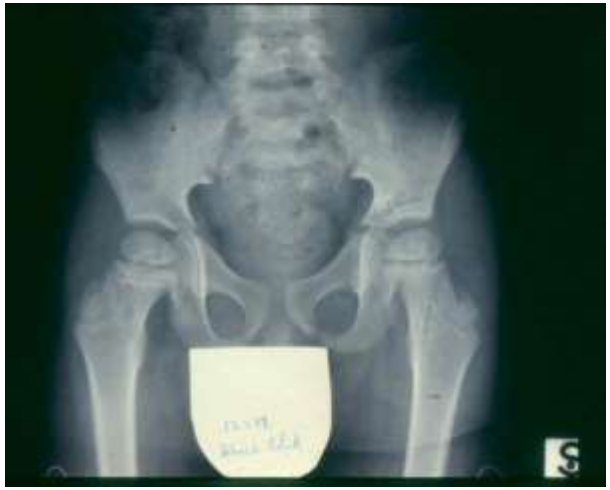
CRMO

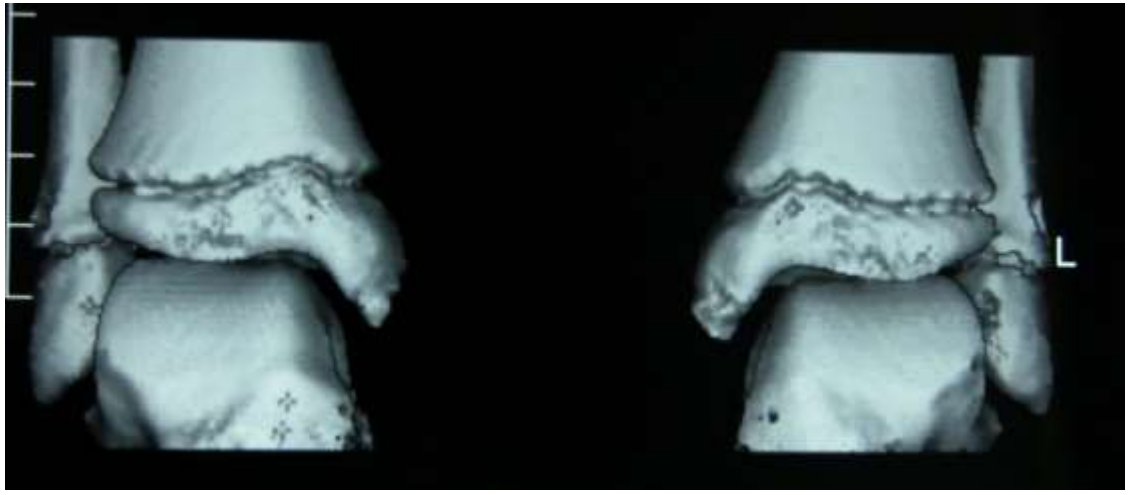


Multifocal, osteomyelitis-like, aseptic, bone lesions





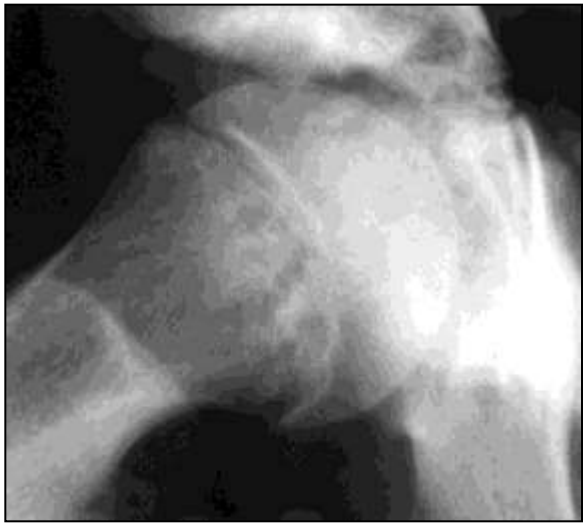




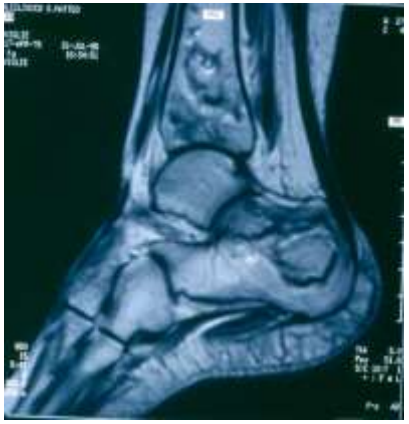
Diseases that can cause articular involvement

- Infectious
- Post-infectious
- Inflammatory
- Hematological
- Neoplastic
- Genetic
- **Orthopedic**

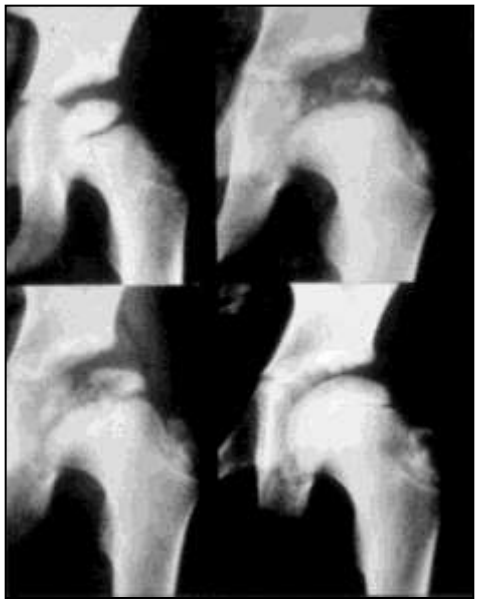
Epiphysiolysis



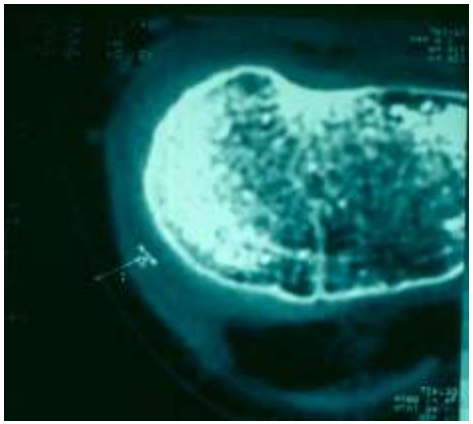
Bone aseptic necrosis



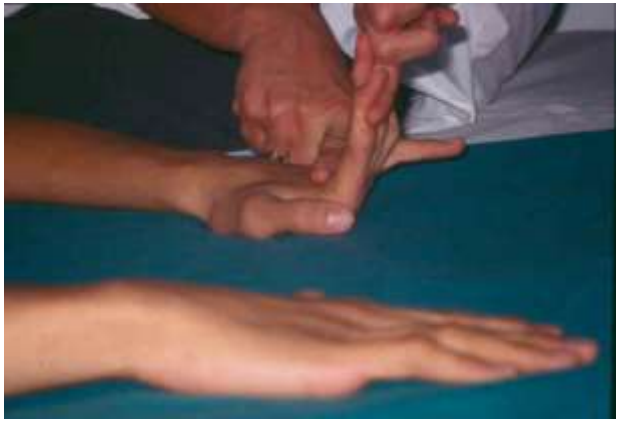
Perthes disease

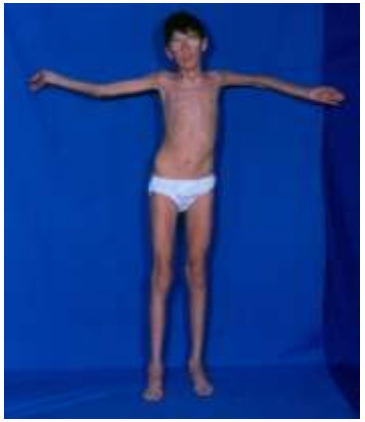


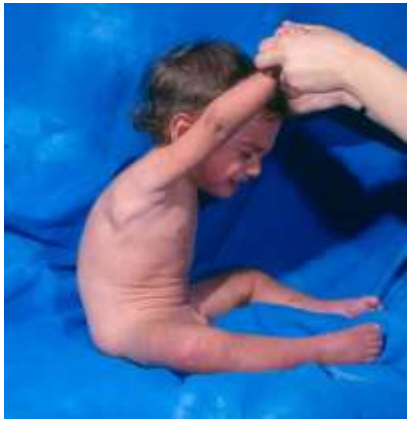
Plant thorn synovitis



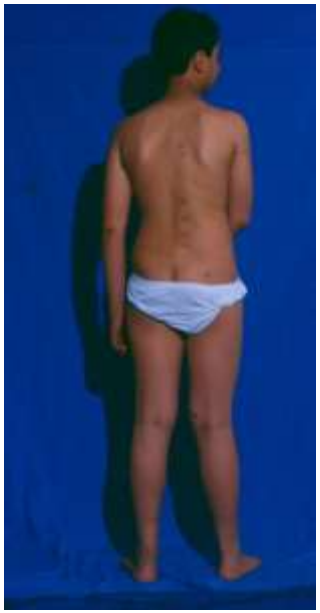
Joint hyperlaxity



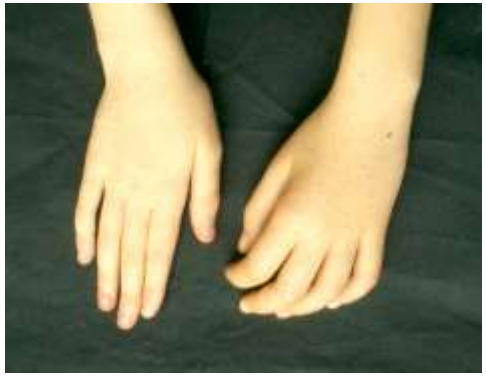


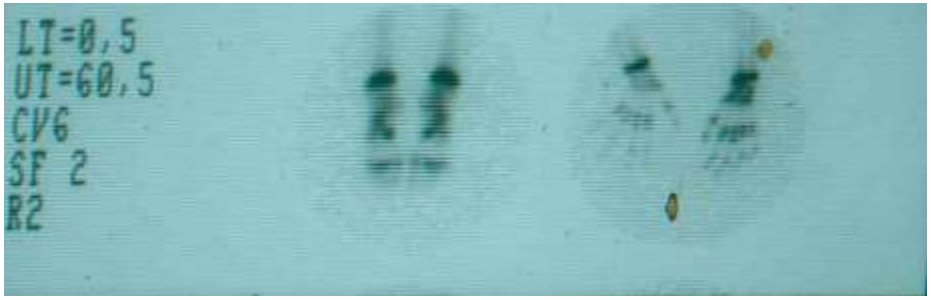


Fibromyalgia

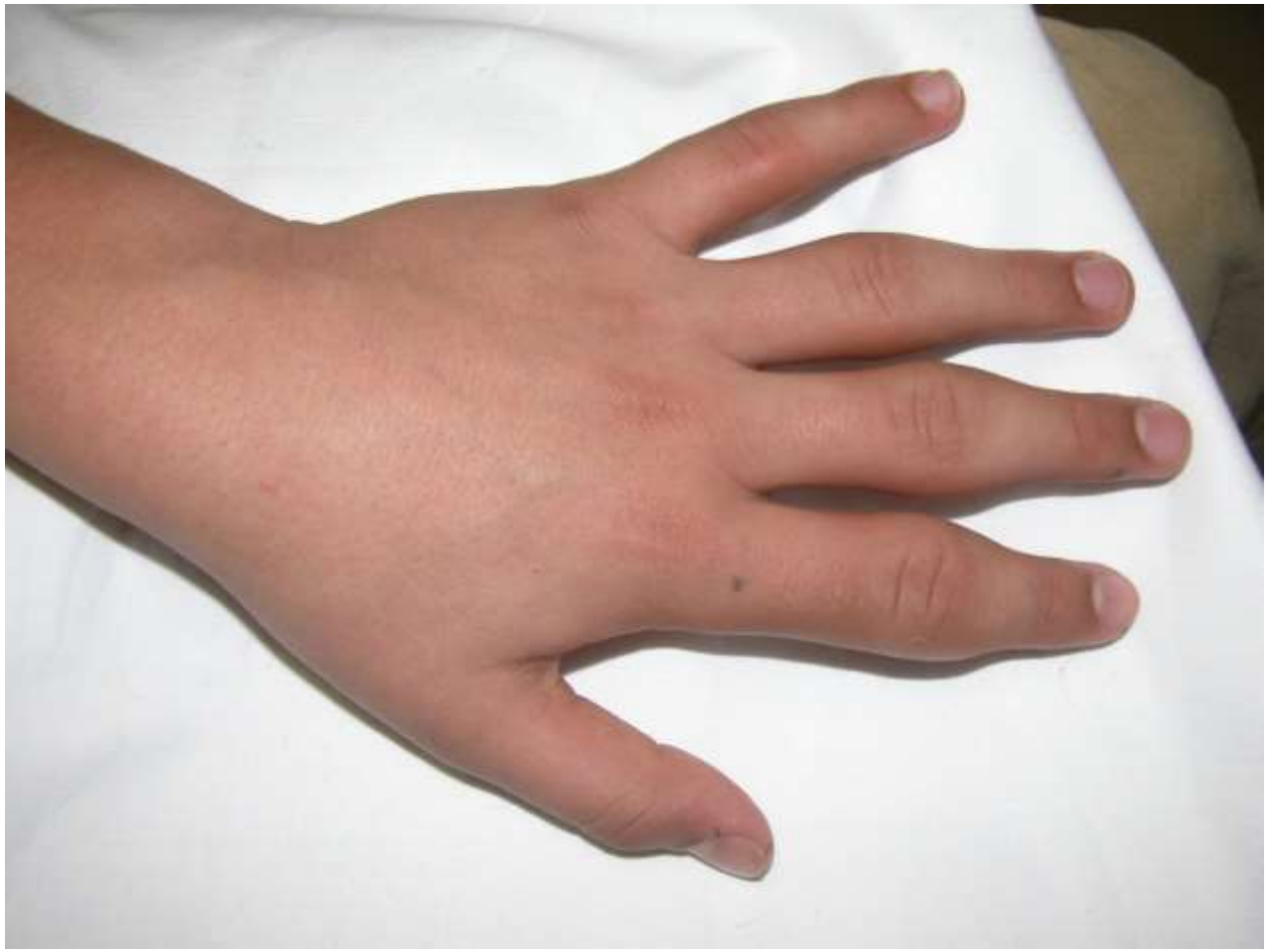


Reflex sympathetic dystrophy





Pachydermodactyly



THANK YOU