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ACUTE VULVAR ULCER AND FEVER IN 16 YEARS OLD GIRL

Martina Bertin, M.D.

C.B. 16 years-old
PARA 0000, mestrual period: irregular, virgin

Intermittent fever (38-40°C)+ sore throat for 7 days

• Dental care one week ago
+ short AB profilaxys with ampicilline 1gr x 2 for one day

• after 4 days with fever, general medicine doctor adviced
Rocefin 1 gr/day i.m. + Azitromicina 500 mg/day

09/06/2015 admission to Emergency Room
(fever + soar throat)

- **ORL** consulence: "AB therapy Rocefin 1gr/day + metronidazole 500 mg x 3/day for 6 days"

11/06/2015 admission to Emergency Room
(vulvar ulcer in septic patient with unknown source of infection)

- **Gynaecologic** consulence: "Single vaginal-vulvar ulcer (1,5 cm diameter) with red and swollen board . The ulcer floor was yellowish.No secretion, no swollen lymph nodes, no other lesion around. Some recurrent aphthous ulcers and patient's mother suffers from psoriasic arthritis. I suggest both reumathologic and infectious disease consultation"

Infectious disease consultation:
" Fever in remission, no rigor nucalis, no skin rush, no joint pain, AB prophylaxis already enhanced, blood coltures results still not ready.
Meanwhile AB therapy as follow: rocefin 1 gr im/day for 7 days, levofloxacina 500 mg 1 cpr/day for 7 days.

Blood samples to check Adenovirus and Echovirus Ab and I strongly suggest reumatologic advice.

Blood and urine sample of 11.06.2015 ER admission:

- BC 13,73 x10.9/L,
- Hb 131 g/L,
- regular kidney and liver function ,
- procalcitonin and lattic acid negative
- **PCR 190 mg/L**

- pregnancy test: negative
- **urine proteins >3 g/L**
- urine Hb 2+ (mestrual period?)
- urine nitrites absent

Blood colture 09/06/2015: negative

Adenovirus sierology 15/06/2015: immune

Echovirus sierology 15/06/2015: not immune

Spontaneous remission of fever, genital ulcer and aphthous ulcers somedays after ER admission…

Nowaday she is well..
….waiting for the results of HLA-B51 and extraction of native DNA for eventual diagnosis of **Behcet Syndrome**

BEHÇET SYNDROME

Behçet syndrome is a **multisystem disease** of unknown etiology .
The syndrome carries the name of the Turkish dermatologist Hulusi Behçet, who, in 1937, described a syndrome of recurrent aphthous ulcers, genital ulcerations, and uveitis leading to blindness.

- **0.3-6.6 cases per 100,000**
- higher prevalence in the Middle East, **China and Japan**,
- affects **men** more commonly than women,
- associated with **HLA-B51**,
- most common among patients from their **third decade** on.

An age of onset younger than 25 years is associated with a higher prevalence of eye disease and active clinical disease.

The aetiology of Behçet's disease remains unknown, but the most widely hypothesis of pathogenesis is that an *inflammatory response is triggered by an infectious agent in a genetically susceptible host*

Marshall SE. Behcet's disease. Best Pract Res Clin Rheumatol. 2004 Jun. 18(3):291-311

BEHÇET CLASSIFICATION

Although Behcet's Disease (BD) is relatively a young disease (described in 1937), it has already **16 sets of diagnosis/classification criteria.** The first of them was proposed by Curth in 1946, then there were the O'Duffy criteria (1974), the International Study Group (ISG) in 1990 and the International Criteria for Behcet's Disease (ICBD) in 2006.

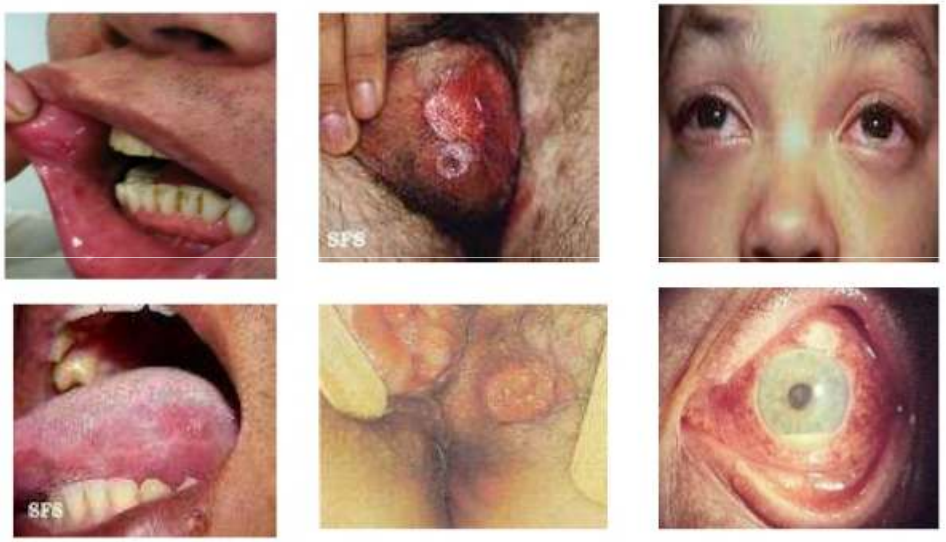
The ISG criteria were created in 1990 to bring a consensus on one set of criteria. During the first International Workshop of Behcet's Disease, it was decided to create the International Criteria for Behcet's Disease,(ICBD) that were presented in Lisbon in 2006.

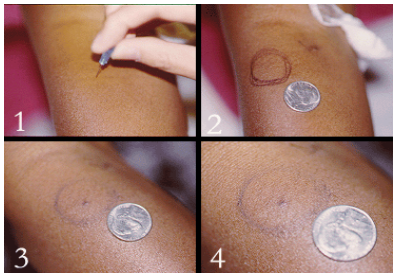
H. O. Curth, "Recurrent genito-oral aphthosis with hypopion (Behcet's syndrome)," Archives of Dermatology, vol. 54, pp. 179–196, 1946. J. D. O'Duffy, "Critères proposés pour le diagnostique de la maladie de Behçet et notes therapeutiques," Revue de Medecine, vol. 36, pp. 2371–2379, 1974.

INTERNATIONAL CRITERIA

Recurrent oral ulcerations + plus 2 of the following:

- Recurrent genital ulcerations
- Eye lesions
  - Anterior uveitis
  - Posterior uveitis
- Cells in the vitreous
- Retinal vasculitis
- Skin lesions
  - Erythema nodosum
  - Pseudofolliculitis
  - Papulopustular lesions
  - Acneiform nodules
- Positive pathergy test





International Team for the Revision of the International Criteria for Behcet's Disease, "Revision of the International Criteria for Behcet's Disease (ICBD)," Clinical and Experimental Rheumatology, vol. 24, supp 42, pp. S14–S15, 2006.

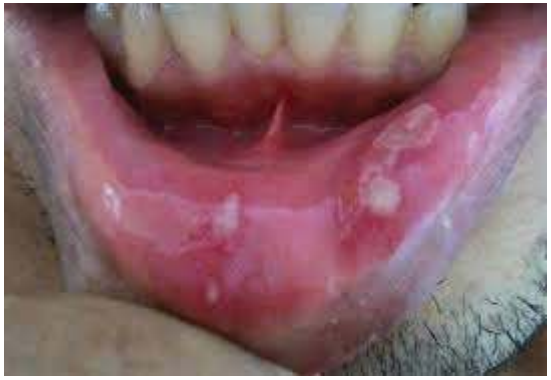
O'DUFFY CRITERIA

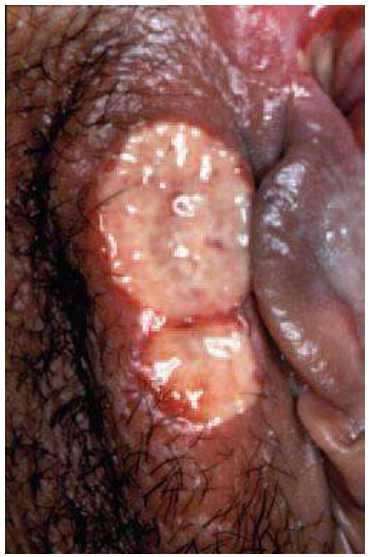
The **O'Duffy criteria** require the presence of recurrent aphthous ulcerations, plus any 2 of following:

- Genital ulcers
- Uveitis
- Cutaneous pustular vasculitis
- Synovitis
- Meningoencephalitis
- *Exclusion of inflammatory bowel disease, systemic lupus erythematosus (SLE), Reiter syndrome, and herpetic infections*

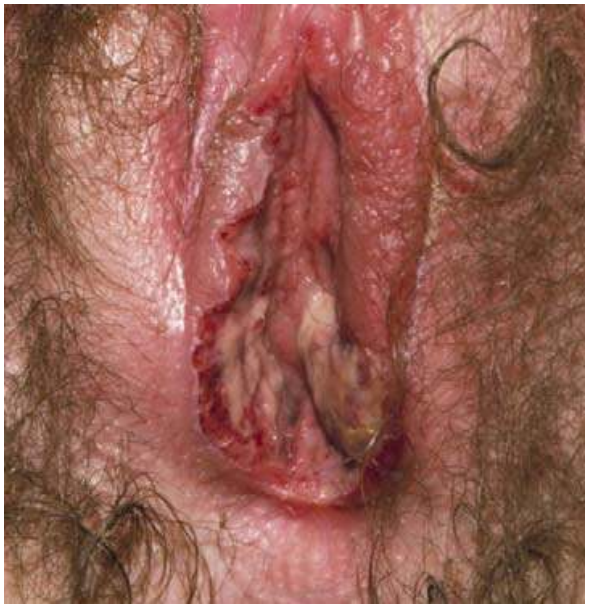
J. D. O'Duffy, "Critères proposés pour le diagnostique de la maladie de Behçet et notes therapeutiques," Revue de Medecine, vol. 36, pp. 2371–2379, 1974.

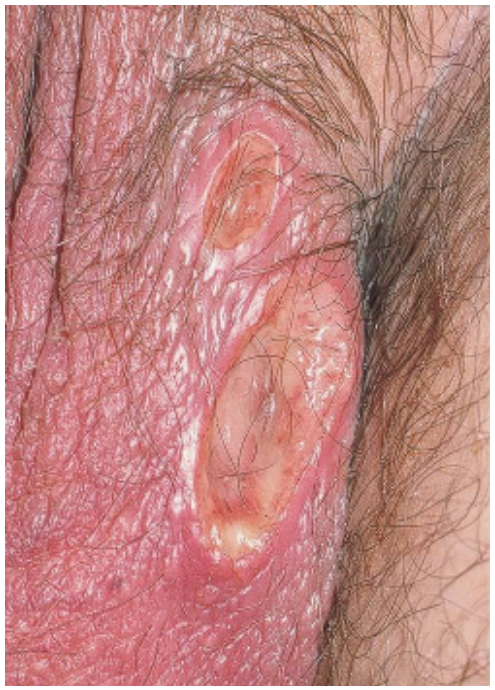
Oral ulceration, the hallmark of this disease, is usually the initial clinical symptom and can precede other manifestations by years. Ulcers are typically painful, appear in crops, and are nonscarring. For diagnostic purposes, *at least 3 episodes in a 12-month period are required*.





Genital ulcers appear in the vulva and vagina in females and scrotum and penis in men. Ulcers are painful, recurring, and scarring.





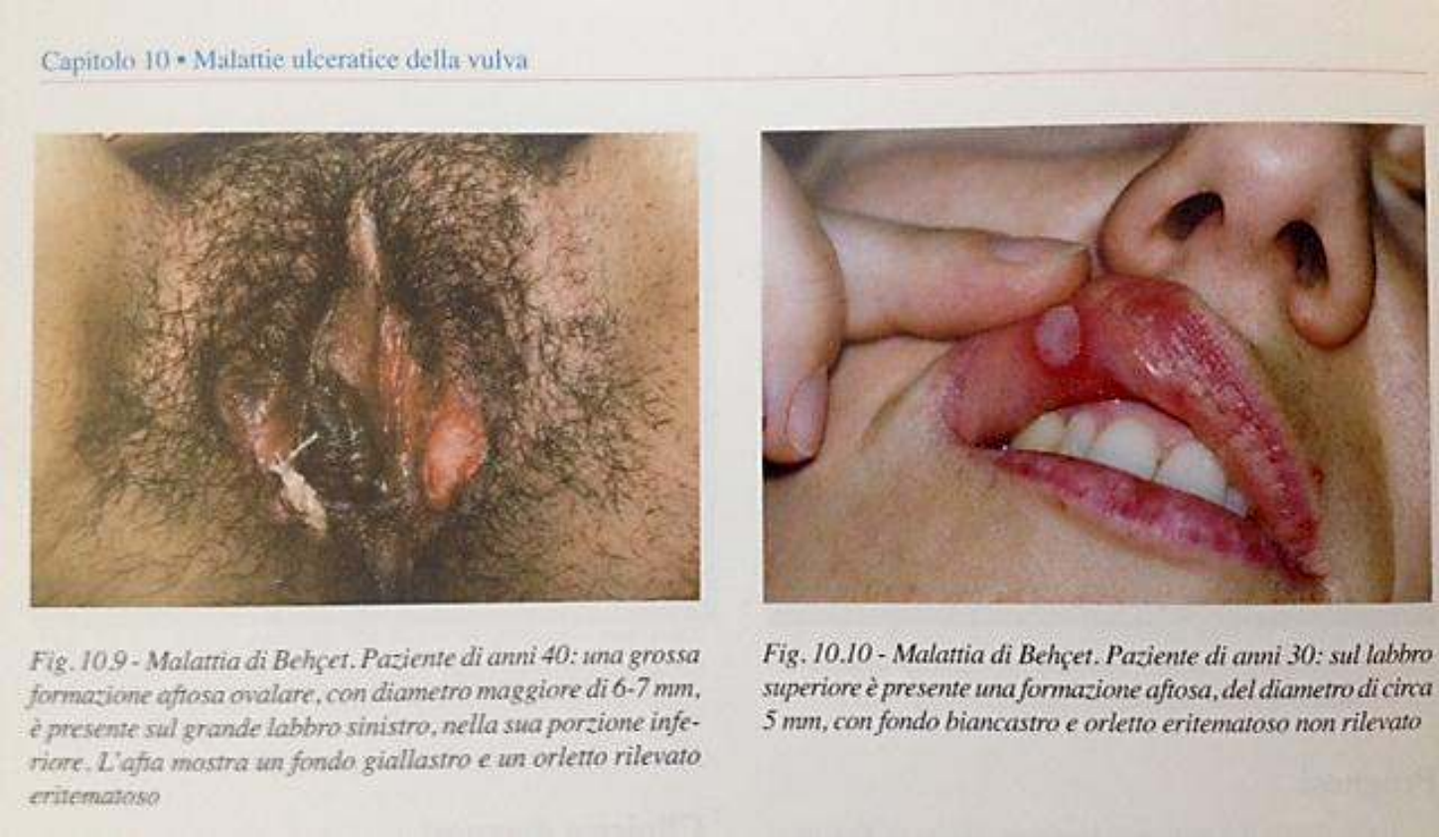


Fig. 10.9 - Malattia di Behçet. Paziente di anni 40: una grossa formazione aftosa ovalare, con diametro maggiore di 6-7 mm, è presente sul grande labbro sinistro, nella sua porzione inferiore. L'afta mostra un fondo giallastro e un orletto rilevato eritematoso

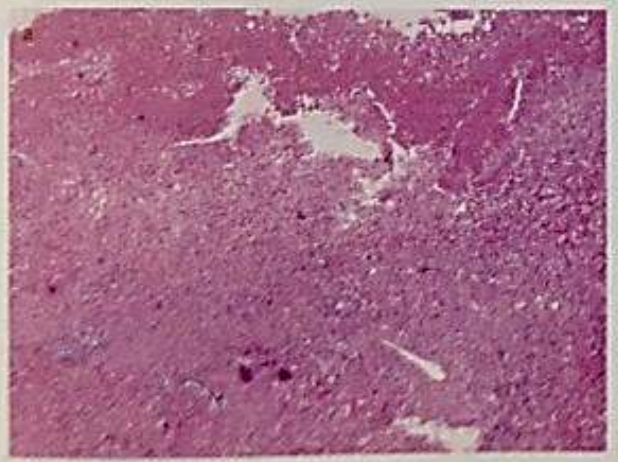
Fig. 10.10 - Malattia di Behçet. Paziente di anni 30: sul labbro superiore è presente una formazione aftosa, del diametro di circa 5 mm, con fondo biancastro e orletto eritematoso non rilevato

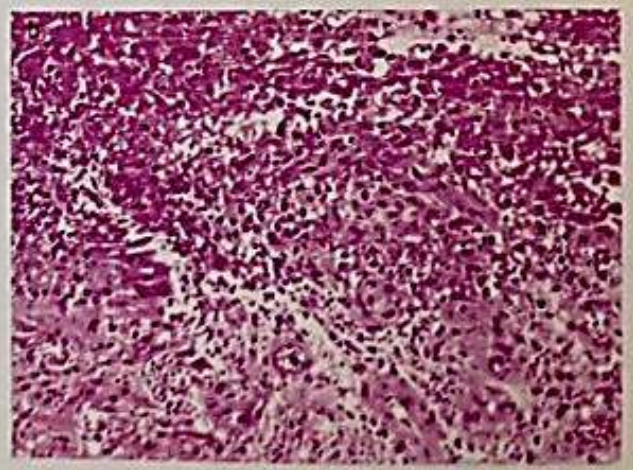
Anglana F et al. Trattato di patologia vulvare con competenze ginecologiche, dermatologiche e psicologiche. SEE-Firenze 2009cc

FINESTRA ISTOPATOLOGICA: MALATTIA DI BEHÇET

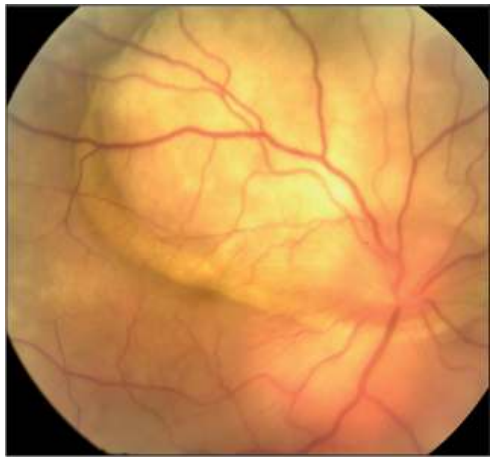
Il quadro microscopico è esente da particolare specificità e presenta un cospicuo infiltrato di linfociti, macrofagi e granulociti neutrofili a livello del pavimento dell'ulcera (Fig. 1a,b).

Focalmente si può osservare esocitosi di elementi linfocitari attivati, con nucleo ingrandito e spesso indentato. A volte cellule coartate si possono osservare in seno all'epitelio marginale dell'ulcera. Nelle fasi precoci non si repertano plasmacellule, mentre tali elementi abbondano nell'infiltrato flogistico delle lesioni più tardive. È inoltre presente un infiltrato infiammatorio che interessa la parete dei vasi di piccole e medie dimensioni; tale infiltrato è composto da elementi linfocitari e granulociti neutrofili con possibile presenza di necrosi e frammentazione dei granulociti stessi (vasculite leucocitoclastica) (Fig. 2).



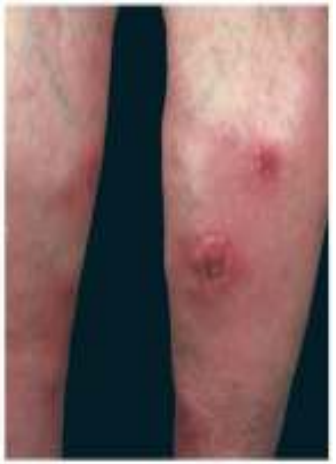


Anglana F et al. Trattato di patologia vulvare con competenze ginecologiche, dermatologiche e psicologiche. SEE-Firenze 2009cc



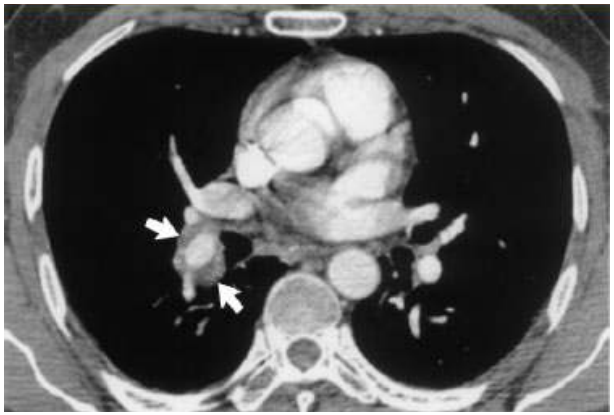
Ocular manifestations may be asymptomatic initially, or may present quite dramatically with hypopyon uveitis.
Anterior uveitis results in pain, blurry vision, light sensitivity, tearing, or redness of the eye.
Posterior uveitis may be more dangerous and vision–threatening because it often causes fewer symptoms while damaging a crucial part of the eye — the retina.

Al-Mujaini A, Wali UK. Frosted branch angiitis, neuroretinitis as initial ocular manifestation in Behçet disease. Indian J Ophthalmol. 2011 May-Jun. 59(3):240-1



Vascular manifestations are varied:

- most commonly secondary to **superficial venous thrombosis**
- large venous occlusions, such as Budd-Chiari syndrome or superior vena-caval syndrome
- cerebral venous thrombosis -> increased intracranial pressure -> headache and visual blurring.
- **arterial occlusions** may present with symptoms related to ischemia

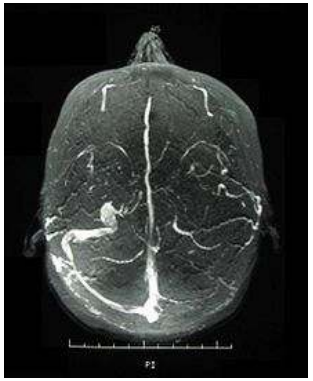


Pulmonary manifestations include pulmonary vasculitis and pulmonary arterial aneurysm formation; patients may present with hemoptysis, chest pain, or cough.

Erkan F, Cavdar T. Pulmonary vasculitis in Behçet's disease. Am Rev Respir Dis 1992;146:232-239

There are two types of **Neuro-Behcet disease**: parenchymal and non-parenchymal. The two types of neuro-Behcet disease rarely occur in the same person. Statistics indicate that approximately 75% BD patients advanced to parenchymal while 17.7% of BD patients advanced to non-parenchymal.

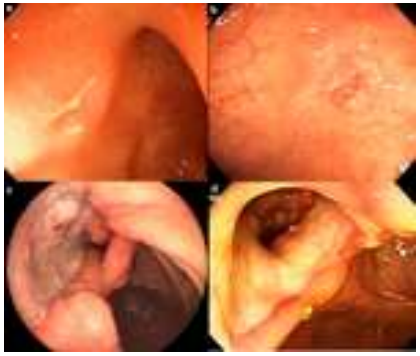
Parenchymal: immune-mediated meningoencephalitis, inflammation of brain, primarily occurs. The target areas include brainstem, spinal cord, and cerebral regions. Sometimes it is hard to determine the affected area because patients are asymptomatic.



In **non-parenchymal** NBD, vascular complications such as cerebral venous thrombosis primarily occur (sinus or cortical), but there could also be aneurysm. In most cases, veins are much more likely to be affected than arteries.

Kidd D, Steuer A, Denman AM, Rudge P. Neurological complications of Behçet's syndrome.1999 Brain ***122****: 2183–94.*

Behçet's disease affects the joints in up to two in every three people with the condition, causing **arthritis-like symptoms** such as pain, stiffness, swelling, warmth and tenderness. The joints most often affected include the knees, ankles, wrists and small joints in the hands.



Gastrointestinal manifestations:
ileo-cecal ulcers are the most commons, but BD may involve any segment of the intestinal tract.
GI manifestations usually occur 4.5-6 years after the onset of oral ulcers. The most common symptoms include abdominal pain, nausea, vomiting, diarrhea and gastrointestinal bleeding

Skef W, Hamilton MJ, Arayssi T. Gastrointestinal Behçet's disease: A review. World Journal of Gastroenterology : WJG. 2015;21(13):3801-3812. Cheon JH et al. Development and validation of novel diagnostic criteria for intestinal Behçet's disease in Korean patients with ileocolonic ulcers. Am J Gastroenterol. 2009 Oct;104(10):2492-9

BEHÇET AND PROGNOSIS

Younger patients and men generally have more severe disease, demonstrating an increased frequency both of mortality and of morbidity related to eye, vascular and neurological. Currently, loss of useful vision is seen in less than 10–15% of patients with eye involvement, compared with 75% of such patients 20–30 years ago. Whereas many patients with BS, especially older females, can be managed symptomatically, the young male with potentially blinding and lethal disease has to be treated aggressively.

Yurdakul S, Yazici H. Behcet's syndrome. Best Pract Res Clin Rheumatol 2008; 22: 793–809.

To summarize, this study adds substantial evidence for gender-associated clinical variation in BD and in particular a clinically meaningful association between male gender and the risk of cardiovascular and ocular involvement.

Bonitsis NG et al. Gender-specific differences in Adamantiades Behcet's disease manifestations: an analysis of the German registry and meta-analysis of data from the literature. Rheumatology 2015;54:121-133

BEHÇET TREATMENT

Table 3 Nine recommendations on Behçet disease (BD) that were developed after two anonymous Delphi rounds

No.	Recommendation
1	Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids.
2	If the patient has severe eye disease defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease (retinal vasculitis or macular involvement), it is recommended that either ciclosporine A or infliximab be used in combination with azathioprine and corticosteroids; alternatively IFNα with or without corticosteroids could be used instead.

Hatemi G et al. EULAR recommendations for the management of Behçet disease Ann Rheum Dis 2008; 67:1656–1662

BEHÇET TREATMENT

3	There is no firm evidence to guide the management of major vessel disease in BD. For the management of acute deep vein thrombosis in BD immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide or ciclosporine A are recommended. For the management of pulmonary and peripheral arterial aneurysms, cyclophosphamide and corticosteroids are recommended.
4	Similarly there are no controlled data on, or evidence of benefit from uncontrolled experience with anticoagulants, antiplatelet or antifibrinolytic agents in the management of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD.
5	There is no evidence-based treatment that can be recommended for the management of gastrointestinal involvement of BD. Agents such as sulfasalazine, corticosteroids, azathioprine, TNFα antagonists and thalidomide should be tried first before surgery, except in emergencies.
6	In most patients with BD, arthritis can be managed with colchicine.
7	There are no controlled data to guide the management of CNS involvement in BD. For parenchymal involvement agents to be tried may include corticosteroids, IFNα, azathioprine, cyclophosphamide, methotrexate and TNFα antagonists. For dural sinus thrombosis corticosteroids are recommended.
8	Ciclosporine A should not be used in BD patients with central nervous system involvement unless necessary for intraocular inflammation.
9	The decision to treat skin and mucosa involvement will depend on the perceived severity by the doctor and the patient. Mucocutaneous involvement should be treated according to the dominant or codominant lesions present.
	Topical measures (ie, local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers.
	Acne-like lesions are usually of cosmetic concern only. Thus, topical measures as used in acne vulgaris are sufficient.
	Colchicine should be preferred when the dominant lesion is erythaema nodosum.
	Leg ulcers in BD might have different causes. Treatment should be planned accordingly.
	Azathioprine, IFNα and TNFα antagonists may be considered in resistant cases.

CNS, central nervous system; IFN, interferon; TNF, tumour necrosis factor.

Hatemi G et al. EULAR recommendations for the management of Behçet disease Ann Rheum Dis 2008; 67:1656–1662

ACUTE GENITAL ULCER

Acute genital ulcers, also known as acute vulvar ulcers, ulcus vulvae acutum or *Lipschütz ulcers*, refer to an ulceration of the vulva or lower vagina of non-venereal origin that usually presents in young women, predominantly virgins.

"an acute onset of flu-like symptoms with single or multiple painful ulcers on the vulva. Diagnosis is mainly clinical, after exclusion of other causes of vulvar ulcers. The treatment is mainly symptomatic, with spontaneous resolution in 2 weeks and without recurrences in most cases. "

Treatment consisted of anti-inflammatory drugs, analgesics and prophylactic broad-spectrum antibiotics (amoxicillin/clavulanic acid and azithromycin).

Delgado-García S.et al. Acute genital ulcers BMJ Case Rep 2014.

Table 1 Differential diagnosis of acute genital ulcers in an adolescent

Infection	
Sexually transmitted	Herpes simplex virus Syphilis Lymphogranuloma venereum Chancroid HIV
Non-sexually transmitted	Herpes simplex virus Epstein-Barr virus Cytomegalovirus Influenza A Paratyphoid
Systemic disease	Crohn's disease Cyclic neutropenia PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis) MAGIC syndrome (mouth and genital ulcers with inflamed cartilage) Iron, folate, vitamin B_{12} deficiency Behçet's disease Pemphigus and pemphigoid Complex and simple aphthosis
Hormone-related	Autoimmune progesterone dermatitis Oestrogen hypersensitivity
Drug reaction	Non-steroidal anti-inflammatory drugs Contact or irritant dermatitis
Malignancy	Lymphoma/leukaemia
Trauma	Foreign body Sexual injury Caustic burns

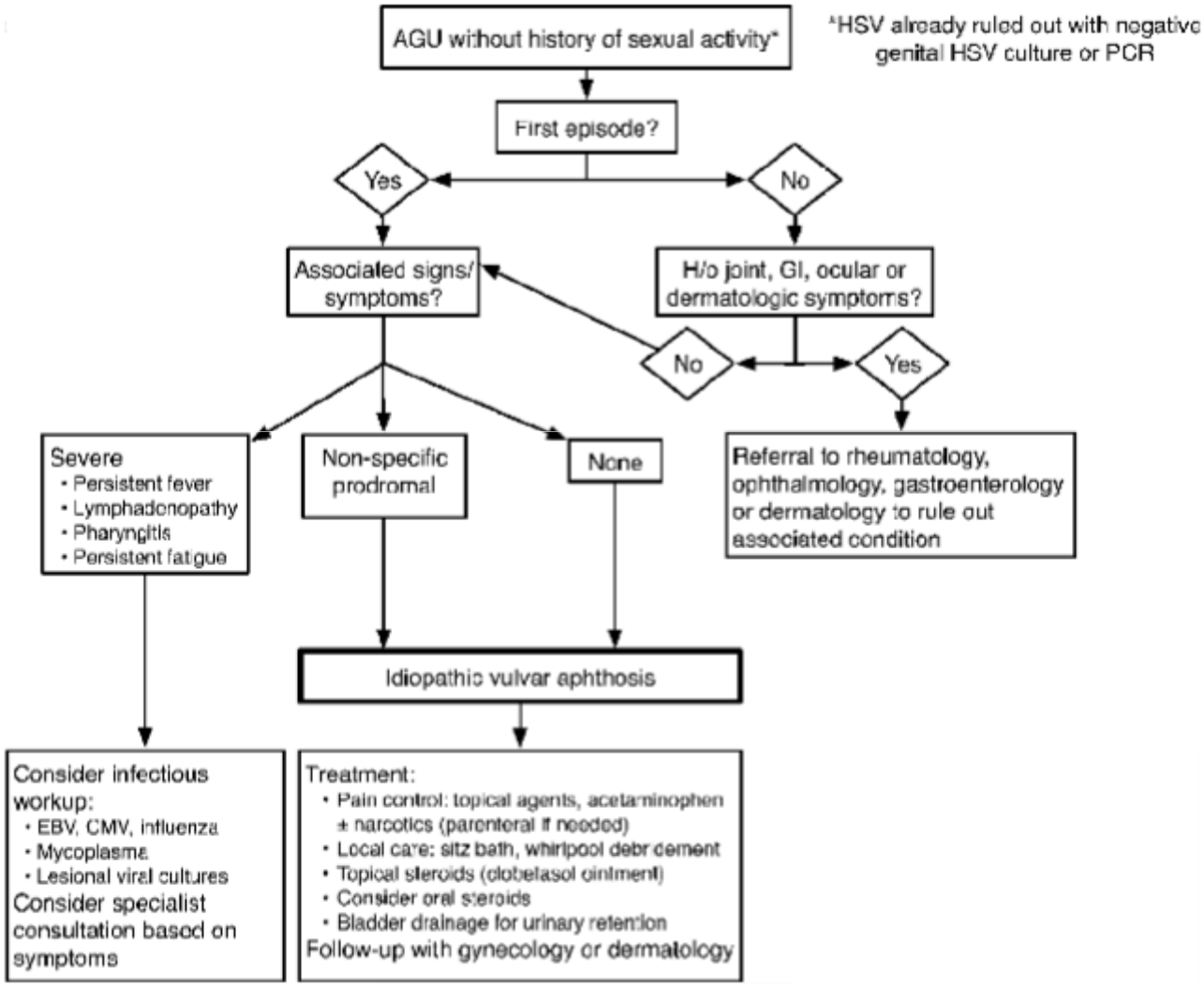
Delgado-García S.et al. Acute genital ulcers BMJ Case Rep 2014.

Trager JDK. Dermatology—What's Your Diagnosis? Recurrent Oral and Vulvar Ulcers in a Fifteen-Year-Old Girl. J Pediatr Adolesc Gynecol (2004) 17:397–401

Table 1. Causes of Vulvar Ulcers in Young Girls and Adolescents

Category of Vulvar Ulcer	Examples
Infectious	Amebiasis[3,15]
	Chancroid
	Deep fungal infection
	Epstein-Barr virus[2,16]
	Herpes simplex virus
	Human immunodeficiency virus
	As primary cause of ulcer[7]
	Due to opportunistic infection (e.g., cytomegalovirus, cryptococcosus[17])
	Leishmaniasis[3]
	Mycobacterial infection
	Osteomyelitis (of pubic symphysis, with draining sinus)[18]
	Paratyphoid fever[19]
	Pseudomonas aeuriginosa (ecthyma gangrenosum, notably with leukemia)
	Syphilis
	"Viral syndrome"[1]
Inflammatory	Behçets disease
	Childhood vulvar pemphigoid[9]
	Complex aphthosis (oral and genital aphthae)
	Cutaneous Crohn's disease[3,4]
	Erosive lichen planus[3]
	Pemphigus vulgaris[3]
	Pyoderma gangrenosum[3]
	Reiter's syndrome[20]
	Vulvitis circumscripta plasmacellularis[21]
Malignancy*	Hemophagocytic syndrome[22]
	Langerhan's cell histiocytosis (histiocytosis X)[23]
	Myelocytic leukemia[8]
Medication-induced	Fixed drug eruption (e.g., non-steroidal anti-inflammatory agents)[3,24]
	Foscarnet[3,25]
	Lithium carbonate[26]
	Potassium permanganate[27]
Trauma	Factitious[3]
	Tampon use[28]

*Other ulcerative vulvar skin malignancies (squamous cell carcinoma, basal cell carcinoma, and melanoma) would be extremely rare in young girls and adolescents.



Rosman IL et al. Acute Genital Ulcers in Nonsexually Active Young Girls: Case Series, Review of the Literature, and Evaluation and Management Recommendations. Pediatric Dermatology Vol. 29 No. 2 April 2012