MAGIC or not MAGIC – does the MAGIC (Mouth And Genital ulcers with Inflamed Cartilage) syndrome really exist ? A case report and review of the literature

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ABSTRACT

Introduction. *In 1985, Firestein* et al. *described 5 patients with relapsing polychondritis and Behçet's disease (BD) and proposed the term "MAGIC" syndrome as an acronym for "Mouth and Genital ulcers with Inflamed Cartilage". We report on an additional case of this syndrome and critically review the literature.*

Results. *From 1985 to 2004 eleven cases of MAGIC syndrome were described. All patients had chondritis and oral aphthous ulcers, as well as ocular inflammation (mainly anterior uveitis or scleritis/episcleritis). Most patients also presented with genital ulcers and arthritis. In one case, aortic aneurysm, in another aortic insufficiency was described, one had meningoencephalitis, one had antiphospholipid syndrome and one was HIV positive. Before 1985, we could find 4 additional probable cases. Our own patient presented with oral and genital ulcers, auricular chondritis and episcleritis. HLA-typing was performed and revealed HLA-B*51, B*15, DRB1*04x and DRB1*11x. Only in one Japanese patient from the literature, HLA-typing was available and revealed HLA-B*56, B*62, DRB1*0406 and DRB1*0901.*

Conclusions. *Relapsing polychondritis is associated with HLA-DRB1*04 suballeles, but not necessarily only with those being associated with RA (DRB1*0401 and 0404). In 2 MAGIC patients these suballeles were found. All patients described in the literature had typical polychondritis, but not all did fulfil the classification criteria for BD. Many features of both diseases overlap and are not specific. As polychondritis is associated with other inflammatory rheumatic conditions such as SLE, spondyloarthropathy, rheumatoid arthritis and systemic vasculitides in 30% of all cases, we suggest that MAGIC syndrome is not a disease entity, but merely the association of BD with polychondritis.*

Introduction

In 1985, Firestein *et al*. (1) described 5 patients with relapsing polychondritis and Behçet's Disease and proposed the term "MAGIC syndrome" (mouth and genital ulcers with inflamed cartilage). Thereafter, 6 additional cases were reported. We report on another case and analyse the HLA-association of the syndrome, discuss the literature and the possibility of Behçet's disease associated with ("secondary") polychondritis.

Case report

In February 2003 a 59 year old male patient of Italian origin presented with oral and genital aphthous ulcers, and relapsing anterior uveitis, polyarthritis and aphthous colitis. Pathergy test was positive. Three weeks after the first symptoms he presented with an inflamed and painful right ear (Fig. 1a) and reddened and painful left eye (Fig. 1b), under treatment with low-dose steroids (20 mg prednisolone) and 100 mg azathioprine which had been started 3 weeks ago. On the forearms, he had typical papulopustules and both elbows were tender and painful with restricted motion. Ultrasound of the elbows revealed synovitis in all compartments bilaterally. The ophthalmologist diagnosed scleritis and prescribed local steroids. Echocardiography and thoracic X ray were uneventful. ESR was 30 mm/hour, CRP 4.53 mg/dl. Liver

Table I. Patient characteristics MAGIC (literature and present case).

Case No. (sex, age)	Chondritis	Oral ulcers	Genital ulcers	Ocular	Skin	Other	HLA	BD before RP?
1[1] (f, 25y)	Unilateral ear Saddle nose	+	+	-	Ulcers, pustules	Thrombophlebitis Arthralgias	n.d.	Y, 8y
2[1], f, 10y	Nasal, ears	-	+	Keratitis	Acneiform Vasculitis	Symmetric polyarthritis Pleurisy Thrombophlebitis	n.d.	Y, 14y
3[1], m, 59y	Ears	+	-	-	-	Abdominal pain, Fever Polyarthritis Thrombosis of abdominal aorta GI ulcers	n.d.	Y, 5 y
4[1], f, 26y	Saddle nose Thyroid cartilage Ears	+	+	« Uveitis »	Pretibial abcesses	Tinnitus, ataxia (neuro-BD?) Polyarthritis Sinus vein thrombosis Deafness	n.d.	Y, 4y
5[1], f, 39y	Saddle nose Aural chondritis	+	+	Conjunctivitis Iritis	Vasulitis	Fevers Diarrhea Deafness	n.d.	Y, 14y
6[15], m, 42y	Ears	+	+	Conjunctivitis Keratitis	Pustules Ulcerations	Arthritis	n.d.	Y, 3 weeks
7[16], m, 22y	Ears, nose	+	+	-	Pseudofolliculitis	Polyarthritis Aortic insufficiency	n.d.	Y, 3y
8[17], f, 28y	Ear, bilateral	+	+	-	-	Polyarthritis Pleurisy Fever Aortic aneurysm	n.d.	Y, 9y
9[18], m, 17y	Ears	+	+	Conjunctivitis	Ulcerations Folliculitis	Deep vein thrombosis Thrombophlebitis ACL-IgGAB +	n.d.	Y, 7y
10[19], f, 39y	Ears	+	+	Keratoiritis	Erythema nodosum Gangrene	Arthralgia Colitis Deafness	B*56, B*15, DRB1*0406/0901	Y, 1y
11[20], m, 38y	Ears	+	+	Conjunctivitis	Papulopustules	Right side weakness Diplopia CNS-vasculitis	n.d.	Y, 9y
12, m, 59 y	Ears	+	+	Scleritis	Pathergy +	Aphthous colitis, polyarthritis	B*51, B*15, DRB1*04x, DRB1*11x	Y, 3 weeks
Probable cases before name "MAGIC" was coined								
13[21], m, 38 y	Ears, nasal	+	n.d.	Bilateral diffuse necrotising scleritis	-	Oligoarthritis	n.d.	Y, 2 months
14[22], f, 23y	Ears, nasal, larynx	+	+	-	Pustules, erythema nodosum	Oligoarthritis Fever	n.d.	No, coincident
15[23], f, 35y	Ear, larynx	+	-	Bilateral keratokonjunctivits	Ulcerations	Arthralgia	n.d.	n.r.
16[24], m, 14 y	Ear	+	Anal	-	-	Fever	n.d.	Y, 3 years (BD incomplete)

Y: yes ; y: years ; n.d.: not done; n.r.: not reported.

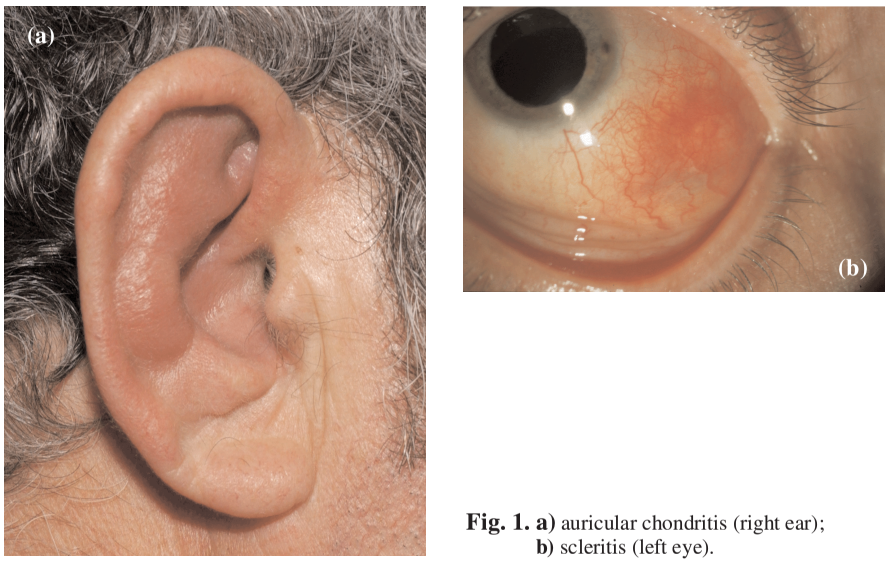

Fig. 1. a) auricular chondritis (right ear); **b)** scleritis (left eye).

enzymes were elevated (azathioprine adverse effect). Virological and bac teriological serologies were uneventful (except antibodies against hepatitis B), autoantibodies (ANA, dsDNA, ANCA, ACL) were negative. HLA-typing revealed HLA-B*51(08 or 20), B*15, DRB1*04x and DRB1*11x. Medication was switched to cyclosporin A and remission was achieved.

Literature research

We performed a PubMed research from 1960 to 2004 with the key indexing terms "Behçet", "polychondritis", and "Magic" syndrome.

Eleven cases described as MAGIC syndrome were found between the first description by Firestein in 1985 and 2004. Before 1985, we could find 4 additional probable cases. All patients already reported as MAGIC syndrome had chondritis and oral aphthous ulcers, as well as ocular inflammation (mainly anterior uveitis or scleritis/episcleritis), and most patients also presented with genital ulcers and arthritis. In one case, aortic aneurysm and in another aortic insufficiency was found. Sterile meningoencephalitis and antiphospholipid syndrome were present in one patient each, and one was HIV positive. HLA typing was performed in one Japanese patient only, and revealed HLA-B*56, B*62 (15), DRB1*0406 and DRB1*0901. In all cases described after 1985, symptoms of BD occurred before polychondritis. The symptoms of the patients found in the literature are depicted in Table I.

Discussion

Relapsing polychondritis (RP) is a rare (annual incidence 3.5 cases per million in Rochester, NY) (2), chronic, potentially fatal multisystem disorder char-

Table II. Classification criteria for polychondritis and Behçet's disease.

International Study Group criteria for Behçet's Disease[25]	McAdam criteria for relapsing polychondritis[3]
1. Bilateral auricular chondritis	1. Recurrent oral aphthous ulcers Minor aphthous, or herpetiform ulceration, observed by physician or patient, which recurred at least 3 times in one 12-month period
2. Nasal chondritis	2. Recurrent genital ulceration Aphthous ulceration or scarring, observed by physician or patient
3. Non-erosive, seronegative inflammatory polyarthritis	3. Eye lesions Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination, or retinal vasculitis observed by an ophthalmologist
4. Ocular inflammation (conjunctivitis, keratitis, scleritis, episcleritis, uveitis)	4. Skin lesions Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesion or acneiform nodules in postadolescent patients not on corticosteroid treatment
5. Respiratory tract chondritis (laryngeal and/or tracheal cartilage)	5. Positive pathergy test Read by a physician at 24 to 48 hours
6. Cochlear and/or vestibular dysfunction (neurosensory hearing loss, tinnitus and/or vertigo)	
7. Cartilage biopsy confirmation of a compatible histological picture	
3 or more must be fulfilled for diagnosis	1. plus 2 others

Table III. Symptoms of polychondritis and Behçet's disease (in percent).

Symptom	Behçet's	R P
Chondritis	-	100
Auricular	-	85
Nasal	-	54
Costochondral	-	2
Laryngotracheal	-	50
Oral ulcers	100	35
Genital ulcers	60-80	10
Arthritis	47-69	50-85
Thrombosis	30	rare
Arterial	5	rare
Venous	95	rare
Arterial aneurysms	5	10
Ocular inflammation	44-79	50
Gastrointestinal	3-30	rare
Audiovestibular	4-15	30
Skin	41-79	50
Pustules	60	30
Erythema nodosum	30	30
Cardiac	1-6	10
Renal	rare	6-22
Central nervous system	10	10

According to Firestein *et al.*[1], McAdam *et al.*[3], Frances *et al.*[9], Letko *et al.*[26] (RP) and Sakane *et al.*[27]

acterised by recurrent episodes of inflammation of cartilaginous tissues. All types of cartilage can be involved, including the elastic cartilage of the ears and the nose, the hyaline cartilage of the peripheral joints, the fibrocartilage at the axial sites and the cartilage at the tracheobronchial tree. Inflammation of other proteoglycan-rich structures, such as eye, heart valves, blood vessels and inner ear also occurs. Systemic symptoms such as fever, weight loss are common and vasculitis affecting skin or internal organs has been described. McAdam (3) developed diagnostic criteria (Table II) which still are used. There is a genetic linkage to HLA-DR4 (DRB1*04 subtype alleles), although not to the same suballeles as those found in RA (4). The pathogenesis of RP seems to be an immunologic reaction to type II collagen, which is present in the sclera of the eye and in cartilage. In patients with RP, both autoantibodies and cellular immune reactions to type II collagen have been shown (5-7). Relapsing polychondritis in approximately 30% is associated with other, mostly autoimmune, diseases.

Behçet's disease (BD) also is a multisystem disorder with the histopathological correlate of a leukocytoclastic vasculitis. It is characterised by recurrent oral ulcerations, genital ulcerations, skin lesions such as papulopustules and erythema nodosum, a non-erosive oligoarthritis, uveitis, and rarely also arterial aneurysms, thrombophlebitis or deep vein thrombosis, and CNS vasculitis (Table III). The prevalence of BD is highest in the Middle East, Asia and Mediterranean countries (up to 350/100.000), but very low in North America and Northern Europe (0.5/100.000). Behçet's disease is associated with HLA-B*51 in 70% of the cases.

There is a considerable overlap between the symptoms observed in BD and RP. In RP, oral aphthous ulcers have been described without any other symptoms of BD, as well as other forms of uveitis than scleritis (anterior, posterior, retinal vasculitis) (8). Skin lesions such as erythema nodosum and papulopustules, and cutaneous leukocytoclastic vasculitis, were also described to occur in RP (9). Firestein, who was the first to describe patients with features of both diseases and created the acronym "MAGIC", already no-ticed this overlap of clinical symptoms (1) (Table III), and discussed a possible similar pathogenesis of both vasculitic diseases encompassing autoimmunity against elastic tissues and cartilage.

On closer inspection, the cases number 2, 3, 8, 13 and 16 would not have fulfilled the classification criteria for BD which today are recommended for classification of BD in studies. This is mainly due to the ocular manifestations, which mostly were described as "keratitis", "conjunctivitis" or "scleritis". All these are common in and typical of RP, but not of BD. In BD, 70% of all patients develop ocular manifestations in the course of their disease. Hypopioniritis, the classic form of iridocyclitis in BD, occurs in 19 to 31 % of all cases, posterior uveitis and retinal vasculitis are the most common forms of ocular involvement in BD (70% of all ocular manifestations). Scleritis, episcleritis and keraititis may also be seen, but are rare (approximately 2 % of all ocular involvements) (10). In contrast, in RP the commonest form of ocular involvement, which occurs in 50% to 60% of the patients (4), are scleritis, episcleritis, keratitis, conjunctivitis, the latter often with consecutive ulcerations, whereas hypopioniritis rarely occurs and posterior uveitis and retinal vasculitis are extremely rare. However, chorioretinitis with consecutive retinal scars can be seen (8, 11, 12).

Hence, all patients described until to date fulfilled the Mc Adam criteria for RP, but five of 16 did not fulfil BD classification criteria. Most of the others, including the one described in the present report, display some unusual features of BD – such as, for example, the late onset of BD in the present case. Usually, BD manifests in people aged 25 to 35, primary manifestations above an age of 50 years are rare.

The results of the present literature survey and the case report do not speak in favour of a similar pathogenesis of both diseases, but for the association of polychondritis with BD. Polychondritis occurred secondary to BD in most cases described in the literature, and in the two cases who were HLA-typed, HLA-DR4 suballeles (associated with RP) were found – our case even also was positive for HLA-B51, which is associated with BD.

Most interestingly, most cases of "MAGIC syndrome" were described in Western Europe and USA, where BD is rare. To date, only one case of this overlap has occurred in a country with a high prevalence of BD (Japan), but not in others such as Turkey, Iran, or other Mediterranean of Middle Eastern countries. This may hint at another ethnical difference in the expression of specific manifestations of BD. Gastrointestinal manifestations, for example, occur much more commonly in Japan than in other countries (13), whereas the pathergy phenomenon is relatively common in Turkey, but rarely positive in the UK or the USA (14).

As in RP immune reactions against collagen can be found in most patients, it seems probable that in the autoimmune diseases which are associated with RP, the inflammatory process which is caused by the underlying ("primary") disease induces damage of elastic tissues or cartilage. Components of the damaged tissues are presented to the immune system (which is not anergic, because these components normally will not be presented to cells of the immune system) and finally the autoimmune reaction against these components (such as collagen type II) leads to the clinical picture of chondritis. In order to prove this and better define the pathogenesis of this association, we would propose to perform HLA-typing in all patients and detect collagen antibodies and/or cellular reactions against collagen whenever possible.

Notably, to date only 12 cases fulfilling classification criteria for both diseases have been described – it is worth discussing if, until considerably more cases with both conditions have been described, this overlap should be given a particular name. We would suggest that the term "MAGIC syndrome" most probably describes polychondritis occurring secondary to BD and thus merely describes another association of an autoimmune disease/vasculitis with RP (BD/RP overlap).

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