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Increased neutrophil chemotaxis. A secondary phenomenon useful in the diagnosis and follow up of diseases with inflammatory component

Y MATZNER,* VERA LEIBOVICI**

Hematology Unit* and Department of Dermatology**, Hadassah University Hospitals, Mount Scopus and Ein Karem, Jerusalem, Israel

The role of the neutrophil chemotaxis assay in clinical medicine is relatively limited. The number of neutrophil defects with decreased chemotaxis is small and they are mainly neutrophil adhesion defects that can be easily screened using a simple adhesion assay. Neutrophil chemotaxis is secondarily decreased in many conditions of chronic inflammation and infection but its study is usually of no clinical importance. Primary defects of increased neutrophil migration were not proved but there are certain conditions that result in secondary increased neutrophil chemotaxis. The following discussion will address several diseases where the increased neutrophil chemotaxis assay may help in diagnosis, follow up and research.

METHODS

Neutrophils were prepared as previously described. Chemotaxis was assayed in Boyden chambers according to the leading front technique using zymosan activated serum as chemoattractant [4]. Results were compared with those of a daily normal control and were expressed as the difference from the normal migration of the same day ("migration"). A difference of 20 μm or more was defined as "increased chemotaxis".

RESULTS AND DISCUSSION

Bechet syndrome

The diagnosis of this rare multisystem disease is based on clinical manifestations in at least three of four cardinal organs: oral and genital ulcers, skin lesions and ocular disease (Table I). However, those manifesta-

TABLE I

Clinical manifestations in patients with Behcet syndrome

Clinical manifestation	Frequency (%)
Oral ulcers	100
Genital ulcers	88
Ocular disease	83
Posterior uveitis	79
Skin lesions	40
Arthritis	36
Vascular involvement	36
Central nervous system involvement	19
Audio-vestibular lesions	5
Epididymitis	2

tions, as well as the involvement of other organs may also occur in other systemic vasculitis. Moreover, many patients suffer from major aphtous ulcerations only and the differential diagnosis from early Behcet syndrome may be difficult. We, therefore, added two parameters for diagnosis: HLA typing and neutrophil chemotaxis [1]. HLA-B51 was present in 71 percent of the patient group as compared with 13 percent of the control group. Neutrophil chemotaxis in this group was enhanced in 80 percent of the patients. Large variability in the results of the chemotaxis assay was found in the B51 – negative group and among the patients with major aphtosis only. Thus, the combination of positive HLA-B51 and increased chemotaxis helps in establishing the diagnosis of Behcet syndrome and may be added as additional criteria especially in partially symptomatic cases. The question whether some of the patients with aphtosis and increased chemotaxis will develop in the future the complete syndrome described by Behcet remains open at the moment and further long follow up is recommended. Moreover, since the finding of increased chemotaxis in Behcet syndrome colchicine therapy was introduced in several patients. This drug inhibits several neutrophil functions, mainly chemotaxis. Consequently, following colchicine treatment the increased neutrophil migration of patients returned to normal and the preliminary impression is that their clinical deterioration slowed down. We believe that, irrespective of the cause for the increased neutrophil migration in Behcet syndrome, it may help in the diagnosis and follow up of this disease and may indicate close observation of selected group of patients with major aphtous ulcerations.

Psoriasis

This common dermatologic disorder is manifested by chronic scaly erythematous plaques. Histologically, there is an epidermal acanthosis and microabsceses composed of neutrophils in the stratum corneum. Several investigators found increased neutrophil chemotaxis in this disease. This phenomenon is probably not a primary defect but is suggested to result from local release of various chemoattractants including C5a, LTB, and PAF in the affected areas [5]. Nevertheless, we used this phenomenon to attempt a new treatment for psoriasis with zinc sulphate. The results shown in Table II suggest that many patients with psoriasis vulgaris expressed increased neutrophil random migration and chemotaxis. The wide range of results, however, limits its use as a diagnostic tool. No such trend could be demonstrated in psoriatic arthritis, where most of the patients had normal neutrophil migration. All of the patients with increased migration responded to zinc sulphate therapy with correction of the chemotaxis assay though the assessment of clinical response needs longer follow up. Thus, in our hands, the chemotaxis assay proved to have

TABLE II

Neutrophil migration in Psoriasis before and after treatment with zinc sulphate

	Migration (μm)	
	random migration	chemotaxis
Psoriasis vulgaris		
before treatment	10.2±11.3*	14.1±14.8*
after treatment	2.1±3.8	0.5±2.2
Psoriatic arthritis		
before treatment	5.8±11.1**	1.1±14.3**
after treatment	2.3±4.0	0.1±6.7

Difference from normal control * $P < 0.05$; ** Non significant

only limited clinical value in selected cases with psoriasis vulgaris and was not useful in psoriatic arthritis.

Sweet's syndrome

This rare dermatologic condition also called "Acute febrile neutrophilic dermatosis" is manifested by systemic fever, neutrophilia and raised painful skin red plaques composed of neutrophils. Since the disease is rare, we had the opportunity to study only limited number of patients [2]. Nevertheless, from our own results and those of others, the following recommendations, concerning the chemotaxis assay, can be suggested (Table III): The patients who express increased neutrophil chemotaxis may respond to drugs that suppress neutrophil activation such as steroids, and possibly colchicine, while the few patients described with normal neutrophil migration may respond to potassium iodide. The neutrophil chemotaxis assay can, therefore, help in therapeutic decisions in these patients.

TABLE III

Therapeutic selection in Sweet's syndrome

Neutrophil chemotaxis	Treatment
Increased	Corticosteroids Colchicine ?
Decreased	Potassium iodide

Familial Mediterranean fever (FMF)

This is an inherited disease affecting Sephardic Jews, Turks, Armenians, and Arabs, in which recurrent episodes of unprovoked inflammation involve the joints and the pleural and peritoneal cavities. The inflammatory episodes last several days, resolve without sequelae and may be prevented with colchicine treatment.

Many studies have been performed in an attempt to understand the basis for the inflammatory attacks in FMF, but a factor capable of inducing both fever and serosal inflammation has not been identified, and immunologic studies have disclosed only nonspecific changes. Although neutrophil func-

tion has generally been found to be normal, measurements of chemotaxis during the course of an acute attack have been described as increased by some investigators while the migration attack free periods was always normal.

As an alternative to those studies it occured to us that FMF might be due to an inherited deficiency of an inhibitory regulator of the inflammatory response. We have recently reported that normal peritoneal and synovial fluids contain a protein (or proteins) that antagonizes the chemotactic activity of the inflammatory mediator complement fragment C5a [4]. In the light of these results, we postulated that the function of this chemotactic inhibitor might be to neutralize small amounts of C5a that might accidentally be released into serosal and synovial cavities during the normal course of events, thus preventing inappropriate episodes of inflammation that would otherwise result from the release of this powerful mediator. Similarly, we reasoned that the acute symptoms of FMF might be associated with a deficiency of this inflammatory regulator [3]. The results in Table IV demonstrate diminished inhibitory activity in peritoneal and synovial fluids of these patients, as compared with normal and osteoarthritic fluids, respectively. These data are in line with our proposal that C5a-inhibitor deficiency in serosal fluids from patients with FMF plays a role in the pathogenesis of the inflammatory attacks characteristic of this disease.

Thus, the neutrophil chemotaxis assay serves as a research tool in FMF but it may also serve as a direct diagnostic aid in showing C5a-inhibitor deficiency in appropriate serosal fluids. It may also estimate colchicine absorption and patient's compliance in the few non responding patients, using colchicine well described anti-chemotactic activity.

Conclusion

A summary of the possible role of the neutrophil chemotaxis assay in the described syndromes appears in Table V. It helps indirectly in the diagnosis of Behcet syndrome as well as in the treatment decision and follow up. Its role in psoriasis is questionable: it does not aid in diagnosis but may sometimes indicate a thera-

Table IV

Inhibition of C5a induced neutrophil chemotaxis by various synovial and peritoneal fluids

Synovial fluids		Peritoneal fluids	
diagnosis	C5a inhibition (%)	diagnosis	C5a inhibition (%)
Osteoarthritis	54.0±1.8	Normal	66.8±4.5
FMF	27.1±4.6*	FMF	6.3±2.8*

* $P < 0.01$

TABLE V

Clinical use of the neutrophil chemotaxis assay

	Diagnosis		Treatment	
	direct	indirect	decision	follow up
Behcet's syn.	—	+	+	+
Psoriasis	—	—	?	?
Sweet's syn.	—	?	+	+
FMF	+	—	—	occasionally

peutic trial with invesigational anti-chemotactic agents. It also has a role in treatment decision in Sweet's syndrome. In FMF, the assay was used as a research tool for clarifying the etiology of this disease; it can also directly prove the diagnosis, assaying serosal fluids, and occasionally may be used to follow up colchicine efficiency in selected cases.

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