

Postsplenectomy type-1 hypersensitivity response: a correlation between IL-4 and IgE serum levels.

Stefano Miniello¹, Graziana Cristallo¹, Mario Testini², Mario Giosuè Balzanelli³,
Rinaldo Marzaioli², Pietro Venezia⁴, Germana Lissidini², Dino Petrozza², Michele
Nacchiero²

¹Section of Emergency and Trauma Surgery, Department of Applications in Surgery of the Innovative Technologies;
²Section of General Surgery and Clinical Oncology, Department of Applications in Surgery of the Innovative
Technologies, ³Postgraduate School in Thoracic Surgery; ⁴2nd General Surgery; University of Bari Medical School,
Bari, Italy.

Reprint requests: Stefano Miniello, MD, Section of Emergency and Trauma Surgery, Department of
Applications in Surgery of the Innovative Technologies - University of Bari Medical School -
Policlinico, P.za Giulio Cesare 11, 70124 Bari, Italy. Tel: +39 080 547 8856.
E-mail: stefanominiello@yahoo.it

Summary

Authors demonstrated the presence of allergic manifestations in splenectomized patients following traumatic rupture of this organs. In particular, allergic diathesis, as supported by serum IgE increase, was exclusively found in patients with preserved T helper (h)-2 lymphocyte function. Th-2 function was monitored by measuring serum levels of interleukin (IL)-4, a cytokine involved in IgE synthesis. On the opposite, in splenectomized individuals with a reduced Th-2 function as supported by lower IL-4 serum levels, no IgE increase and allergic manifestations were detectable. On these grounds, authors hypothesize that allergic manifestations may be correlated to splenectomy since its exeresis may favour the persistence of antigens in the blood. Consequentially, in patients with a preserved Th-2 function, antigenic overload may lead to IgE increase and allergy onset.

Key words

Allergy, IgE, Interleukin-4, Splenectomy.

Introduction

Splenectomy is a very old surgical procedure since the very first splenectomy was performed by Andriano Zancarello in 1549, as reported by Wilkins⁽¹⁾. However, only in the last century the immunological role of the spleen was emphasized by Morris and Bullock⁽²¹⁾, who described a lethal sepsis in splenectomized rats in comparison to controls. Later on, higher frequency of infectious episodes as well mortality due to sepsis were reported in splenectomized children with spherocytosis⁽³⁾. Also in adults postsplenectomy sepsis was observed and, in particular, in veterans from the second world war^(4,5).

Therapeutically speaking, in 1920 Marine and Manley⁽¹⁵⁾ investigated the possibility of homotransplanting the spleen in splenectomized rats to prevent the risk of sepsis. Over the past years, it is just worthwhile mentioning a report by Corazza et al.⁽¹⁶⁾ who demonstrated that recovery of splenic function needed an implant of at least 30 cm³ of tissue. Nowadays, the therapeutical trend is to apply a conservative treatment in patients with traumatic rupture of spleen even if, initially, Rosoff and associates⁽¹⁷⁾ pointed out the risk related to the conservative treatment in splenic traumas. Nevertheless, conservative therapy appears to be more consolidated also in view of the better knowledge of surgical anatomy of the spleen and the accurate selection of patients according to more sophisticated of diagnostic procedure.

Over the past decades, the better knowledge in the field of immunoregulation has also clarified the role of the spleen. In fact, in this organ, previously considered as a sort of non specific filter on the bloodstream, many specific immune responses can occur. More specifically, besides macrophage-dependent phagocytosis antigen presentation and generation of antigen-specific clones of T and B lymphocytes can take place. On these grounds, one can easily understand the septic complications following splenectomy and, in particular, the outcome of overwhelming post-splenectomy infection (OPSI)⁽⁶⁾. Our recent studies⁽⁷⁻¹⁰⁾ on splenectomized patients have revealed a series of immunological alterations still detectable after many years from the surgical event. Besides deficits of phagocytosis and killing exerted by granulocytes and monocytes, also an altered release of cytokines, such as interferon (IFN)- γ and IL-4, was reported⁽⁷⁻¹⁰⁾. Usually, these deficit are underestimated, thus leading to severe complications in the course of stressful conditions such as surgery, burns, various traumas and infections⁽¹¹⁻¹⁴⁾. In this framework, we reported that skin tests could represent a very easy and valid diagnostic tool for detecting a condition of immunodeficiency in splenectomized patients^(7,8). In this work, in a group of splenectomized patients affected by allergic manifestations levels of serum IgE and IL-4 were measured. Results indicate that allergic manifestations in splenectomized patients correlates with increase levels of serum IgE and normal or augmented serum amounts of IL-4.

Patients and methods

We evaluated 16 patients (13 men and 3 women; age range between 18 and 50 years) who underwent splenectomy for traumatic, non pathologic, rupture of the organ.

Inclusion criteria:

- age range: 18-65 years;
- $\Delta t > 6$ months since operations, to avoid bias in the immune status evaluation, related to: surgical procedure¹⁴, anesthesia¹⁵, intraoperative blood loss¹⁶, and blood transfusions.

Exclusion criteria:

- Age over 65 years to avoid immunosenescence effects¹⁷⁻²⁰;
- pathological splenic rupture;
- hematological, lymphoid or immunosuppressive diseases.

The trial was conducted according to the following steps:

- I. Clinical history with particular attention to previous sepsis or infectious diseases;
- II. Clinical examination
- III. Serum measurement of IL-4
- IV. Serum measurement of Ig E
- V. Skin tests

IL-4 was assayed in sera with a commercial kit (Pharmigen, USA) according to manufacturer's instructions.

Serum Ig E measurement was assayed by ELISA

Skin tests were performed with a commercial kit (ALK, Denmark) according to manufacturer's instructions.

Results

As indicated in table 1, according to clinical history, postsplenectomy allergic manifestations (conjunctivitis, dermatitis, rhinitis), were recorded in 9 out of 16 patients (56%). Conversely, according to present clinical examination allergic manifestations were observed in 8 out of 9 patients (50%) (Table 1). Allergic manifestations were distributed as follows: dermatitis (4 patients), rhinitis associated with conjunctivitis (2 patients), dermatitis associated with conjunctivitis (1 patient), dermatitis associated with rhinitis (1 patient).

Higher values of IgE were present in 8 out of 16 patients studied (Table 1). Among patients with normal levels of IgE only one, despite a negative clinical examination, exhibited a previous clinical history consistent with allergic disease.

IL-4 serum concentration was normal in 6 patients (37,5 %), higher in 2 (12,5%) while in the remaining 8 cases (50%) it was lower than normal values (Table2).

Increased levels of serum IgE corresponded to normal or increased levels of IL-4. On the contrary, serum concentration of IgE was within normal ranges in the presence of undetectable or lower levels of IL-4.

Quite interestingly, in patients with lower levels of IL-4 no evidence of previous allergic manifestations was recorded, as well as clinical examination excluded this type of pathology (data non shown).

Discussion

In 9 out of 16 splenectomized patients we found allergic manifestations either in the clinical history or at the moment of clinical examination. Our results clearly demonstrate that postsplenectomy allergy as an expression of immediate hypersensitivity response correlates with serum Ig-E levels and normal or augmented serum concentration of IL-4. In fact in the absence or in the presence of low amounts of IL-4 serum Ig-E levels are normal and, mostly, allergic manifestations are absent.

Our data add novel findings to the hot topic related to the postsplenectomy complications. Even if the pathogenesis of postsplenectomy-mediated allergic manifestations deserves further investigation and clarification, according to the present data the following hypothesis can be formulated. Splenectomy represents a clinical condition in which the daily antigenic load not efficaciously cleared by the reticuloendothelial system thus allowing the persistence of antigens in the host. In particular, among antigens microbial components are responsible for severe sepsis such as OPSI also in view of the immunocompromised status in splenectomized patients^(6,8). In fact, in our previous reports, we described either quantitative or qualitative peripheral immune deficits in splenectomized individuals, which may explain the pathogenesis of OPSI or of gram-negative sepsis⁽⁷⁻¹⁰⁾.

According to current literature, pathogenic mechanisms responsible for allergic manifestations in splenectomized individuals can be either genetic or environmental. Inheritance of IgE-mediated reactions seems to be dependent on polymorphism in the IL-4 gene which leads to immediate hypersensitivity responses⁽¹⁸⁾. At the same time, allergic individuals, when immunized with non allergic antigens, such as tetanus toxoid, produce a larger number of Th₂ clones, thus leading to an exaggerated release of IL-4 in comparison with non allergic individuals^(19,20). In synthesis, allergic individuals are programmed toward a Th₂ response with heightened IgE production, regardless of the type of antigenic stimulus. Therefore, in splenectomized patients with an inherited tendency to generate immediate hypersensitivity reactions (IgE-mediated), circulating non allergic antigens may trigger allergic manifestations. These data emphasize the role of the spleen in the clearance of a number of antigens otherwise deleterious in the host. Additionally many evidences support the role of environmental factors in the enhancement of immediate hypersensitivity reactions.

Experimentally, in rodents non specific adjuvants such as bordetella pertussis, cholera toxin are able to upregulate IgE responses, thus altering the pattern of T cell activity⁽²¹⁾. Polyaromatic hydrocarbons from diesel exhaust (PAH-DEP) were shown to enhance IgE production from B cells in the presence of IL-4 and CD40 ligand⁽²²⁾. In vivo intranasal application of PAH-DEP in humans led to a specific enhancement of IgE, as measured in terms of increase in mRNA and IgE-forming cells in the nasal lavage⁽²³⁾. Taken together, all these data emphasize the role of adjuvants in the enhancement of immediate hypersensitivity reactions with expression of clinical allergic disease in individuals genetically susceptible who, however, might not develop allergy. With special reference to splenectomized patients, the lack of antigenic clearance may lead to dissemination of various types of adjuvants into the host, thus leading to a frank clinical illness.

Conclusively, in the light of our data, a periodical laboratory and clinical monitoring of splenectomized patients for diagnosis of immediate hypersensitivity reactions needs to be performed, even after many years from surgery.

Table 1: IgE levels and allergic manifestations in splenectomized patients.

PATIENTS	IgE kU/l*	Allergic manifestations in the Clinical History	Clinical Examination
DBO	224 ↑	Dermatitis	Dermatitis
CC	36	Absent	Absent
EF	28	Absent	Absent
CN	32	Absent	Absent
VC	236 ↑	Dermatitis and Rhinitis	Dermatitis and Rhinitis
CV	41	Conjunctivitis	Absent
CM	177 ↑	Rhinitis and Conjunctivitis	Rhinitis and Conjunctivitis
DMR	196 ↑	Dermatitis and Conjunctivitis	Dermatitis and Conjunctivitis
SS	168 ↑	Dermatitis	Dermatitis
LF	30	Absent	Absent
MMF	37	Absent	Absent
SE	188 ↑	Dermatitis	Dermatitis
LG	183 ↑	Rhinitis and Conjunctivitis	Rhinitis and Conjunctivitis
IL	27	Absent	Absent
RD	176 ↑	Dermatitis	Dermatitis
SG	34	Absent	Absent

* Reference values: 0-100 kU/l

↑ Above normal values

Table 2: IgE and IL-4 profiles in splenectomized patients

PATIENTS	IgE kU/l*	IL-4 pg/ml**
DBO	224	25,1 ↑
CC	36	0 ↓
EF	28	1 ↓
CN	32	0 ↓
VC	236	24,7 ↑
CV	41	0 ↓
CM	177	4 =
DMR	196	9.9 =
SS	168	4 =
LF	30	2 ↓
MMF	37	2 ↓
SE	188	9 =
LG	183	6 =
IL	27	0 ↓
RD	176	6 =
SG	34	1 ↓

* Reference values: 0-100 kU/l

** Reference values: 7.5 ± 3.4 pg/ml

↑ Above normal values

↓ Below normal values

= Within normal values

ACKNOWLEDGMENTS

Paper supported by a grant from MIUR (Rome, Italy)

REFERENCES

- 1 - WILKINS BS
The spleen. Historical review.
Br. J. Haematol. 2002 May;117(2):265-74.
- 2 - MORRIS DH, BULLOCK FD
The importance of the spleen in resistance to infection.
Ann. Surg. 1919 November; 70(5): 513–521
- 3 - KING H, SHUMACKER HB Jr
Splenic studies. I. Susceptibility to infection after splenectomy performed in infancy
Ann. Surg. 1952 Aug;136(2):239-42
- 4 - SINGER DB
Postsplenectomy sepsis.
Perspect. Pediatr. Pathol. 1973 ;1: 285-311
- 5 - ROBINETTE CD, FRAUMENI JF Jr
Splenectomy and subsequent mortality in veterans of the 1939-45 war.
Lancet. 1977 Jul 16; 2(8029):127-9
- 6 - DIAMOND LK
Splenectomy in childhood and the hazard of overwhelming infection.
Pediatrics. 1969 May; 43(5):886-9.
- 7 - MINIELLO S, JIRILLO E, URGESI G, D'ABBICCO D, TOMASICCHIO N
BONOMO GM.
Cell-mediated immunity and delayed hypersensitivity study in splenectomized patients:a comparative evaluations between IFN-gamma and skin tests
Chir. Ital. 1999 Jul-Aug; 51(4):289-92.
- 8 - ALTAMURA M, CARADONNA L, AMATI L, PELLEGRINO NM, URGESI G,
MINIELLO S.
Splenectomy and sepsis: the role of the spleen in the immune-mediated bacterial clearance.
Immunopharmacol. Immunotoxicol. 2001 May; 23(2):153-61.

- 9 - MINIELLO S, TESTINI M, JIRILLO E, PICCINNI G, URGESI G, LISSIDINI G, ANGRISANO A, TOMASICCHIO N, BONOMO GM.
Postsplenectomy immunodepression and its implications: an underestimated problem.
Int. Surg. 2002 Oct-Dec; 87(4):245-51
- 10 - JIRILLO E, MASTRONARDI ML, ALTAMURA M, MUNNO I, MINIELLO S, URGESI G, AMATI L.
The immunocompromised host: immune alterations in splenectomized patients and clinical implications.
Curr. Pharm. Des. 2003; 9(24):1918-23
- 11 - MARINE D, MANLEY O.T.
Homotransplantations and autotransplantation of the spleen in rabbits
J. Exp. Med. 1920; 32:113
- 12 - CORAZZA GR, TAROZZI C, VAIRA D
Return of splenic function after splenectomy: how much tissue is needed?
Br. Med. J. (Clin Res Ed) 1984 Oct 6; 289(6449):861-4
- 13 - ROSOFF L, COHEN J.L, TELFER N, HALPERN M.:
Injuries of the spleen.
Sug. Clin. North. Am. 1972; 52 (3): 667-85
- 14 - BEREMBAUM MC, COPE WA, BUNDICK RV.
Synergistic effect of cortisol and prostaglandin E₂ on the PHA response:
Relation to immunosuppression induced by trauma.
Clin. Exp. Immunol. 1976 Dec; 26(3):534-41
- 15 - STANLEY TH, HILL GE, PORTAS MR, HOGAN NA; HILL HR.
Neutrophil chemotaxis during and after general anesthesia and operation.
Anesth. Analg. 1976; 55(5):668-73
- 16 - JUBERT AV, LEE ET, HERSH EM, McBRIDE CM.
Effects of surgery, anesthesia and intraoperative blood loss on immunocompetence.
J. Surg. Res. 1973; 15(6):399-403
- 17 - MINIELLO S.
Immunologic implications of surgical intervention in critical and noncritical patients .
Recenti Prog. Med. 1991; 82(10):561-7

- 18 - BARNES KC, DUFFY DL, NEELY JD, FREIDHOFF L, BREAZEALE DL, SCHOU C, NAIUDU RP, LEVETT PN, RENAULT B, KUCHERLAPATI R, IOZZINO S, EHRLICH E, BEATY H, MARSH DG.
Linkage analysis of IL-4 and other chromosome 5q31.1 markers and total serum immunoglobulin concentrations.
Science 1994; 264:1152-1156
- 19 - WIERENGA EA, SNOEK M, DE GROOT C, CHRETIEN I, BOS JD, JANSEN HM, KAPSENBERG ML.
Evidence for compartmentalization of functional subsets of CD4⁺ T lymphocytes in atopic patients.
J. Immunol. 1990; 144:4651
- 20 - PARRONCHI P, MACCHIA D, PICCINNI MP, BISWAS P, SIMONELLI C, MAGGI E, RICCI M, ANSARI AA, ROMAGNANI S.
Allergen - and bacterial antigen- specific T-cell clones established from atopic donors show a different profile cytokine production.
Proc. Natl. Acad. Sci. USA 1991; 88:4538
- 21 - KEMENY DM, NOBLE A, HOLMES BJ, DIAZ-SANCHEZ D.
Immune regulation: a new role for the CD8⁺ cell.
Immunol. Today 1994; 15:107
- 22 - MACAULAY AE, DE KRUYFF RH, GOODNOW CC, UMETSU DT.
Antigen-specific B cells preferentially induce CD4⁺ T cells to produce IL-4.
J. Immunol. 1997 May; 158(9):4171-9.
- 23 - TAKENAKA H, ZHANG K, DIAZ-SANCHEZ D, TSIEN A, SAXON A.
Enhanced human IgE results from exposure to the aromatic hydrocarbons in diesel exhaust: direct effects on B cell IgE production.
J. Allergy Clin. Immunol. 1995 Jan; 95:103-15
- 24 - DIAZ-SANCHEZ D, DOTSON AR, TAKENAKA H, SAXON A.
Diesel exhaust particles induce local IgE production in vivo in humans and alter the pattern of IgE mRNA isoforms.
J. Clin. Invest. 1994; 94:1417