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Autoinflammatory/autoimmunity syndrome induced by adjuvants (Shoenfeld's syndrome) in patients after a polypropylene mesh implantation

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A B S T R A C T

In both hernia repair and pelvic organ prolapse surgery, polypropylene (PP) meshes are increasingly used. Although these technologies offer tremendous clinical benefits, the efficacy of these implants can be hindered by the body's immunologic reaction to the implanted material. Undesirable local effects such as chronic pain have been extensively described. Systemic effects, however, are not yet reported. Because systemic effects after implantation of other biomaterials have been described, we evaluated patients with implanted PP meshes for signs and symptoms of biomaterial-related systemic illnesses.

Patients referred to an Autoimmunity Clinic between January 2014 and December 2017 were analyzed. In 40 patients, mesh implants were present. These patients were evaluated for the development of a systemic illness.

Thirty-two consecutive women and eight men were included in the current study. Median age at the time of operation was 49.5 years (range, 28–75 years). Eighteen patients had a hernia repair and 22 patients had a vaginal mesh implant. Thirty-nine of 40 patients presented with chronic fatigue, and 38 of 40 patients had myalgia or muscle weakness. In most patients, these symptoms started shortly after the operation. All patients fulfilled the diagnostic criteria for autoinflammatory/autoimmunity syndrome induced by adjuvants (ASIA). In addition, most patients reported localized pain and (often-invalidating) irritable bowel syndrome. One quarter of the patients had an immunodeficiency, whereas a

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diagnosis of well-established systemic and/or localized autoimmune diseases was made in 45% of patients. Importantly, 75% of patients had a pre-existing allergic disease. In 6 patients, the hernia mesh could be completely removed, thereby resulting in (partial) recovery of the systemic disease.
In conclusion, 40 patients developed symptoms of a systemic illness after a mesh operation. All patients fulfilled the diagnostic criteria for ASIA. One quarter of the patients had an immunodeficiency, whereas in approximately half of the patients, an autoimmune disease developed. We postulate that PP mesh implants may increase the risk of developing (auto)immune diseases by acting as an adjuvant.

The occurrence of diseases in which the immune system turns against its host has long been held a special fascination, dating back to the time of Paul Ehrlich [1,2]. During the last decade, it has been recognized that autoinflammation ("Horror Autoinflammaticus"), immunodeficiency, and autoimmunity ("Horror Autotoxicus") represent axes of a multidimensional phenotype that may affect humans [3]. Both autoinflammatory and autoimmune disorders are characterized by aberrant changes in both innate and adaptive immunity that may lead from an initial inflammatory state to an organ-specific damage. Autoimmunity occurs upon a failure of the immune system to recognize the self-environment and a consequential reaction against its own cells and tissues, whereas autoinflammatory diseases are driven by abnormal innate immune activation, which results, for instance, in the activation of the inflammasome [4].

A genetic predisposition has been found to be a prerequisite to develop these immune-mediated diseases. Importantly, environmental factors have been shown to play a role in the pathogenesis of these diseases, and various environmental factors have been linked to these immune-mediated diseases. Well-studied examples in humans are infections, smoking, vaccines, and silica, whereas mercury, in particular, has been extensively studied in experimental animals [5].

During the last decade, it became clear that implanted foreign body materials such as silicones may also be a triggering agent [6]. Silicones are used in a variety of medical applications such as breast implants, hydrocephalus shunts, catheter lines, intraocular implants, rhinoplasty, hearing aids, laryngotracheal stenosis and various other stents, joint implants, testicular prosthesis, and others. Silicones were introduced in the 60s and were thought to be biologically inert. However, during the last 50 years, it became clear that silicones can induce various immunological effects.

These effects are best studied in patients with silicone breast implants (SBIs) [6]. After SBIs, local and distant complications of the SBI procedure have been reported. Local complications of SBI are pain, swelling, redness, infections, capsular contracture, implant rupture, and gel bleeding through the intact capsule. Furthermore, general complications occur, such as arthralgias, fatigue, immune deficiency, autoinflammatory, and autoimmune diseases [6]. Typically, patients with general symptoms that might be related to SBI present with chronic fatigue, arthralgias/arthritis, myalgias and/or muscle weakness, pyrexia, dry eyes and/or a dry mouth, cognitive symptoms, and, sometimes, severe neurological manifestations such as ischemic cerebral disease or a multiple sclerosis-like syndrome [6,7]. These symptoms received during the last 50 years several different names: human adjuvant disease, siliconosis, silicone incompatibility syndrome, silicone-induced toxicity, and, more recently, autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [6–9]. Both patients and doctors suspect that these complaints are caused by the implants. Indeed, removal of the SBI results in an amelioration of symptoms in 60–80% of the patients [10]. It is currently postulated that SBIs cause an inflammatory reaction and that silicon-containing particles are transported to regional lymph nodes, resulting in a pronounced adjuvant effect [6].

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Because other implanted biomaterials may also act as an adjuvant resulting in the enhancement of the adaptive immune response to an autoantigen, we speculated that a polypropylene (PP) mesh could also act as a trigger for ASIA, immune deficiency, and autoimmunity.

The implantation of a synthetic mesh to repair weak tissues started in the 1940s. In 1963, PP mesh was first used to perform a tensionless hernia repair of abdominal wall defects [11]. The tension-free prosthetic repair of every groin and/or abdominal hernia further popularized in the 1980s and since then constituted a major and indispensable share of the care of such defects. At present, it is estimated that there are more than 20 million hernia repair procedures per year worldwide. PP mesh repair is the standard for most repairs, but because of the high costs of a commercial mesh, a sterilized mosquito net mesh is used to prevent hernia recurrence in low- and middle-income countries with more or less similar results than the PP mesh. The price of this low-cost mesh is generally less than 1/1000 the price of a commercial PP mesh [12].

From the early 1990s, the transvaginal implantation of a PP mesh was also used to reinforce a weak pelvic floor for indications such as stress urinary incontinence (SUI) and pelvic organ prolapse (POP). Furthermore, midurethral mesh slings using a PP tension-free vaginal tape (TVT) have become a globally established procedure for managing female SUI [13].

Therefore, PP mesh use in hernia repair and in POP surgery clearly offer clinical benefits, but the efficacy of these implants is hindered by the body's immunologic reaction to the implanted material. Undesirable local effects have been extensively described. Systemic effects, however, are not yet reported. To evaluate the presence of systemic effects in PP mesh-implanted patients, we started a prospective study with a special focus on the presence of ASIA, immune deficiency, and/or autoimmune diseases.

Patients and methods

All patients referred to my autoimmune clinics (Reinaert Clinic, Maastricht, The Netherlands; Maria Hospital, Overpelt, Belgium; or Kaye Edmonton Clinic, Edmonton, AB, Canada) between January 2014 and January 2018 were evaluated for symptoms suggestive of an (systemic) autoimmune disease in the presence of a PP mesh.

A total of 714 patients were studied, and in 40 of them, mesh was present. To obtain cumulative clinical details of the patients, patients were evaluated according to a protocol with emphasis on signs and symptoms of the respiratory tract and abdominal, kidney, ocular, cutaneous, central nervous system, peripheral nerve, cardiac, and musculoskeletal involvement [14]. In addition, special attention was paid to symptoms of ASIA (Table 1) [6–9]. Furthermore, the occurrence of recurrent infections was evaluated.

Table 1
Criteria for the diagnosis of autoimmune/inflammatory syndrome induced by adjuvants (ASIA).

Major criteria
- Exposure to an external stimulus (infection, vaccine, silicone, or adjuvant) before clinical manifestations
- The appearance of “typical” clinical manifestations:
  - Myalgia, Myositis, or muscle weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, unrefreshing sleep, or sleep disturbances
  - Neurological manifestations (especially those associated with demyelination)
  - Cognitive impairment, memory loss
  - Pyrexia
  - Sicca (dry mouth and/or dry eyes)
- Removal of the inciting agent induces improvement
- Typical biopsy of the involved organs

Minor criteria
- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e., irritable bowel syndrome)
- Specific HLA (i.e., HLA DRB1 or HLA DQB1)
- Evolvement of an autoimmune disease (i.e., multiple sclerosis or systemic sclerosis)

Patients are considered to have ASIA when either two major or one major and two minor criteria are present.

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At physical examination, a full examination was performed with special attention paid to the presence of lymphadenopathy and livedo reticularis [15].

The following laboratory tests were performed: C-reactive protein, hemoglobin, leukocyte and eosinophil count, thrombocyte count, alanine aminotransferase level, serum creatinine level, angiotensin-converting enzyme level, creatine kinase (CK), antinuclear antibodies [16], antineutrophil cytoplasmic antibodies (ANCA) [17] https://link-springer-com.ezproxy.ub.unimaas.nl/article/10.1007%2Fs12026-013-8401-3 - CR16), IgM rheumatoid factor [18], anticardiolipin antibodies [19], and immunoglobulin levels (IgG, IgM, IgA, IgE, and IgG subclasses).

Patient classification

Patients were classified as having clinical symptoms compatible with ASIA if they had systemic manifestations such as chronic fatigue, arthralgia, myalgias, pyrexia, sicca symptoms, cognitive impairment, ischemic neurologic disease, and/or symptoms of a demyelinating disease. Patients were classified as suffering from ASIA when Shoenfeld's criteria for this syndrome were fulfilled (Table 1) [8]. In short, four major and four minor criteria were evaluated, and when either two major or one major and two minor criteria were present, the patient was considered having ASIA. Standard diagnostic criteria were used for autoimmune diseases [18–20]. Finally, patients were classified as suffering from immunodeficiency, when total IgG levels were below 6.0 g/L or as IgG subclass deficiency when total IgG was >6.0 g/L but when either IgG1 (<4.0 g/L), IgG2 (<1.3 g/L), or IgG3 (<0.4 g/L) level was decreased [9]. Total IgE levels were considered to be elevated when levels were above the 90% limit of the levels as observed in nonallergic individuals of the same age and sex [21].

Results

Approximately 700 patients were evaluated, and in 40 of them, mesh implants were present. These patients were evaluated according to the protocol, and laboratory tests were performed.

Thirty-two consecutive women and eight men were included in the current study. Median age at the time of evaluation was 49.5 years (range, 28–75 years). Eighteen patients had a hernia repair, and 22 patients had a vaginal mesh implant (four patients had TVT because of SUI; eighteen patients had PP mesh placement because of POP).

Thirty-nine of 40 patients presented with chronic fatigue, and 38 of 40 patients had myalgias or muscle weakness (Table 2). In 61% of the patients, these symptoms started shortly after the operation, whereas in the other patients, signs and symptoms developed later on (i.e., up to 4 years after operation). Sixty-one percent of the patients experienced symptoms within 1 year after mesh implantation, 25% of the patients between one and three years after the operation, whereas in 14% of them, symptoms started more than three years after the implantation.

Typically, patients were already tired when they woke up, whereas most patients also reported post-exertional malaise. Other complaints that were frequently observed included arthralgias (36 of 40 patients), pyrexia (32 of 40 patients), cognitive impairment (31 of 40 patients), and dry eyes/dry mouth (34 of 40 patients) (Table 2). In addition, 7 of 40 patients had stroke-like symptoms. Fifteen percent of patients had clinical ASIA scores of 7 out of 7, 35% had a clinical score of 6 out of 7, 35% had a clinical score of 5 of 7, and 15% had a clinical score of 4 or lower.

Table 2
Symptoms in 40 patients with a systemic illness after mesh implantation.

39/40 patients with fatigue
38/40 patients with myalgias/muscle weakness
36/40 patients with arthralgias/arthritis
31/40 patients with cognitive symptoms
32/40 patients with pyrexia
34/40 patients dry eyes/dry mouth
7/40 patients stroke-like symptoms

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Seventy-eight percent of patients reported that the mesh caused (often severe) pain, and 80% of the patients had complaints of (often invalidating) irritable bowel syndrome (Fig. 1). At physical examination, livedo reticularis was found in 48% of the patients, whereas lymphadenopathy (swollen, tender lymph nodes) was found in 75% of the patients. Importantly, 75% of patients had a pre-existing allergic disease that often deteriorated after the mesh operation.

Laboratory examinations revealed (nonspecific) abnormalities in virtually all patients (Fig. 2). An elevated C-reactive protein (CRP) and/or an elevated angiotensin-converting enzyme (ACE) level and/or an elevated creatine kinase (CK) level was frequently found. In addition, approximately one quarter of the patients had an immunodeficiency as defined by a decreased IgG level and/or decreased levels of IgG subclasses. Autoantibodies (i.e., antinuclear antibodies, ANCA, and/or anticardiolipin antibodies) were found in 38% of patients.

Thirty-three of 40 patients presented with symptoms compatible with fibromyalgia and/or chronic fatigue syndrome/myalgic encephalomyelitis. The other 7 patients presented with an inflammatory arthritis and/or myositis. A diagnosis of well-established systemic and/or localized autoimmune diseases was made in 45% of patients. Four patients developed polymyalgia rheumatica (in one patient accompanied by giant cell arteritis); one patient developed MPO-ANCA vasculitis; and five patients developed connective tissue diseases such as Sjogren's syndrome (n = 2), antiphospholipid syndrome (n = 1), rheumatoid arthritis (n = 1), or polymyositis (n = 1).One patient developed sarcoidosis, and two patients developed *de novo* psoriasis. Finally, five patients developed organ-specific autoimmune diseases (Hashimoto n = 5; pernicious anemia n = 2).

In 19 patients, re-operations were performed. Transvaginal mesh could only partially be removed, which resulted in a decrease of pain but without a clear effect on systemic symptoms. In six patients with a mesh implantation because of hernia, the mesh could be completely removed resulting in (partial) recovery of the systemic disease. In two cases, a histological analysis of the mesh was performed. In both cases, a foreign body reaction with granulomatous inflammation was observed. In none of the patients, a (non-Hodgkin) lymphoma was diagnosed.

Two patients died during follow-up. Both patients had severe weight loss with abdominal pain that was considered by them to be not bearable resulting in suicide.

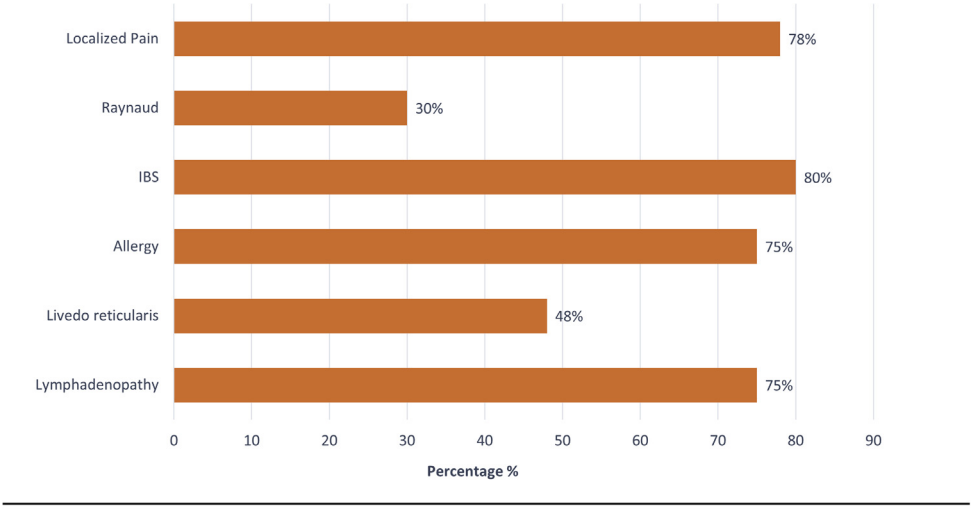
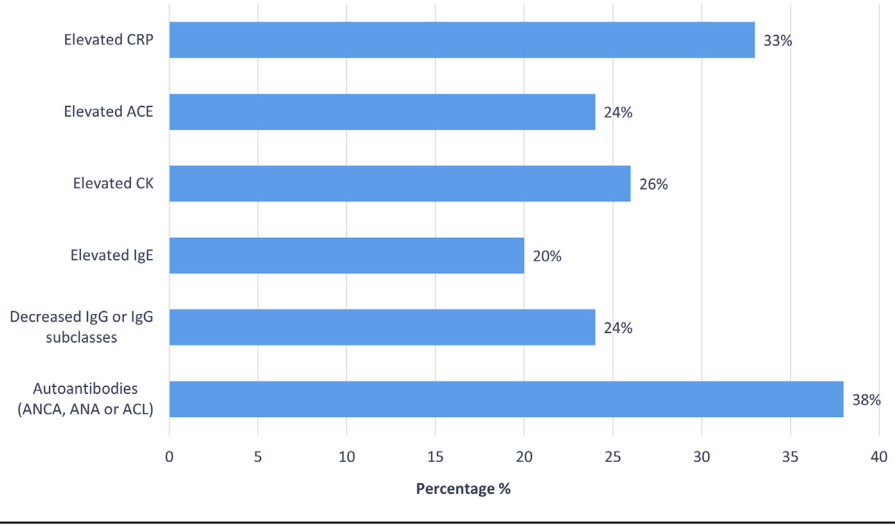


Fig. 1. Additional findings in 40 patients with mesh implants and systemic symptoms.



ACE angiotensin converting enzyme, ACL anti-cardiolipin antibodies, *ANA* antinuclear antibodies, *ANCA* anti-neutrophil cytoplasmic antibodies, *CK* creatine kinase, *CRP* C-reactive protein, *Ig* Immunoglobulin

Fig. 2. Laboratory findings in 40 patients with mesh implants and systemic symptoms.

Discussion

Forty patients developed symptoms of a systemic illness after a mesh operation. All 40 patients had complaints of fatigue, myalgias, and/or other nonspecific symptoms. Furthermore, in approximately half of the patients, an autoimmune disease developed, and in approximately a quarter of the patients, an immunodeficiency was present. Importantly, in nearly all patients, a history of allergies was present.

It is well known that implantation of a PP mesh may result in local complications. After hernia repair, 10–20% of patients have chronic postoperative pain [22]. Furthermore, 2% of patients experience recurrence of the hernia [23]. Importantly, sometimes, severe complications occur, such as chronic infection, dysejaculation, sexual pain, orchialgia, transmigration into adjacent structures, small bowel obstruction, recurrent abscess, and/or fistula formation [23]. Additionally, mesh or TVT placement for POP or SUI may result in major complications such as refractory chronic pain, loss of sexual function, urethral obstruction, organ erosion and/or perforation, bowel injury, bleeding, fistula, and/or abscess formation. Furthermore, in SUI, at least 5% of patients have persistent SUI after TVT placement [24]. An important cause for these complications is that PP meshes induce a local inflammatory response, which may become chronic [25].

The occurrence of a systemic disease in patients with a mesh, however, has not been reported before. According to our observations, we postulate that the implanted PP mesh induced an inflammatory response that caused the systemic illness as observed in other conditions in which biomaterials are implanted [6,26].

Immediately after implantation of a biomaterial such as a PP mesh, a layer of host proteins is adsorbed resulting in the attraction of phagocytes (predominantly macrophages of the pro-inflammatory M1 subtype) [27]. Importantly, this process is critically dependent on the presence of activated mast cells and histamine [28]. Histamine may play a pivotal role in the (often severe) pain that these patients may develop at the site of implantation, as histamine may sensitize the transient reporter potential channel V1 (TRPV1), one of the nociceptors [29]. Furthermore, biomaterials may act

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as an adjuvant resulting in the enhancement of the adaptive immune response to an auto-antigen [30]. Therefore, it can be postulated that the systemic illness in patients with a mesh is a variant of the *autoimmunity/autoinflammatory syndrome induced by adjuvants* (ASIA) as described by Shoenfeld and Agmon-Levin in 2011 [8].

Previously, Bernard-Medina et al. [31] described a patient with an exacerbation of dermatomyositis four months after mesh implantation. The authors postulated that the PP mesh acted as an adjuvant and hence triggered the exacerbation of the underlying autoimmune disease. Indeed, foreign materials such as silicone-breast implants, silicones in other materials, mineral oils, and prosthetic materials used for arthroplasty are known to cause a systemic disease with clinical features as seen in ASIA [6,26,32–34]. Importantly, virtually, all implanted materials are able to induce a foreign body giant cell reaction [35–37]. Furthermore, the biomaterial may deliver a "danger signal" to the immune system and subsequently result in an enhanced immune response [38,39]. As such, the biomaterials act as an adjuvant in the development of an adaptive immune response to an antigen (reviewed in Ref. [30]).

In our study, we found that patients presented with chronic fatigue that was not alleviated by rest. Consequently, patients had a substantial reduction in the ability to engage in levels of occupational, educational, social, and/or personal activities compared to their ability before the illness started. Sleep disturbances such as problems in falling asleep and/or staying asleep were often also present. Probably related to these symptoms are the symptoms of cognitive impairment resulting in memory deficits, absent-mindedness, word-finding difficulties, and difficulty in paying attention.

Another frequently occurring symptom is the occurrence of arthralgias or arthritis (present in 90% of the patients). Most patients fulfill the 2016 criteria for fibromyalgia [40]. In addition, more than 90% of the patients have myalgias and/or muscle weakness and approximately 80% of the patients reported a flu-like syndrome with fever ("pyrexia").

Importantly, 85% of the patients had sicca symptoms, i.e., dry eyes and/or a dry mouth. Sicca symptoms are often severe and may result in blurred vision, keratitis sicca, and/or gum disease.

Symptoms in our patients were not different from those in patients with ASIA due to other causes [7,41,42]. In 2011, Shoenfeld and Agmon-Levin described ASIA with the aim of delineating a common pathway of autoimmune pathogenesis in genetically prone individuals exposed to an adjuvant [43]. In these patients, other environmental factors such as infections and/or vitamin D [44] may attenuate the disease process and as such determine outcome. Because the symptoms as observed in our patients are commonly occurring in the community [45], it can be argued that the relation between mesh and symptoms may be spurious, most likely the result of random events or confounding rather than causality [46]. In addition, some argue that patients may develop these symptoms through a mass psychosis mechanism and that press releases may escalate the occurrence of these nonspecific symptoms [47]. Although these hypotheses are not well scientifically based on observations, these are difficult to reject. Importantly, however, as in SBI [7,10], complete removal of the mesh implant resulted in the recovery of the patient as we observed in six of our patients.

Furthermore, we found that 45% of our patients developed a well-defined autoimmune disease such as rheumatoid arthritis and/or Sjogren's syndrome after mesh implantation, suggesting that the PP mesh in these patients may have acted as an adjuvant resulting in the development of these autoimmune diseases in patients who were genetically predisposed to develop such disease.

In our study, we found that apart from ASIA and autoimmune diseases, many patients had an immunodeficiency defined as either hypogammaglobulinemia or an IgG subclass deficiency. The finding that approximately 25% of our patients with mesh implants have a humoral immunodeficiency is, to our knowledge, new and has not been reported before. As IgG levels were not measured before the mesh implant operation, we cannot exclude that immunodeficiencies in our patients were already present before the implant operation and actually were a risk factor to develop autoimmunity. Anyhow, in patients with mesh implants, PP may stimulate the occurrence of an autoimmune disease when a dysregulation of the humoral immune response is present [48]. Further prospective studies should be performed to study the association between IgG levels and mesh implant operations.

As observed in patients with SBI, patients with a mesh who developed systemic symptoms nearly always had a history of allergies [6,49]. Additionally, as observed in SBI, patients with systemic disease nearly always have local symptoms such as (severe) pain. It has been suggested that postherniorrhaphy pain in these patients is partly caused by the local inflammation resulting in nerve ingrowth into the

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mesh [23]. An important finding in our study is that IBS in mesh-induced ASIA is much more frequent and much more severe than that in SBI-induced ASIA. As mentioned above, this may partly be explained by the local release of histamine that may activate TRPV1 and hence cause an exacerbation of IBS in patients who were previously suffering from (subclinical) IBS [29]. Otherwise, IBS-like symptoms may be caused by the migration of a mesh, and removal of the mesh in such cases may result in the curation of IBS [50].

Mesh implants are placed to repair defects of the abdominal wall and/or to repair a weak pelvic floor, and PP is the most commonly used mesh material, resulting in satisfactory anatomic and functional outcomes in most of the patients who had undergone the operation. Worldwide, more than 20 million PP meshes are placed annually. As an alternative, biological mesh derived from tissue has been safely used for hernia repair, but there is consensus that more studies are needed before they can be considered a good replacement for a PP mesh [51]. Synthetic PP mesh is durable but does not stretch and contract, resulting in stiffness and pain. Indeed, well-known local complications of mesh implants are chronic postoperative pain, recurrence of the hernia and/or SUI, chronic infection, and/or transmigration of the mesh into adjacent structures. During the last decennium, it has been questioned whether the risks of foreign body implantations using PP mesh outweigh the benefits [52–54]. In the present paper, we describe a new complication of mesh implantation, i.e., the occurrence of ASIA. Importantly, we found that patients with a history of allergies are particularly at risk to develop this complication.

An important limitation of the current study is that only patients with complaints who were referred to an autoimmunity clinic were evaluated, whereas the number of patients who have undergone such a mesh implantation uneventfully is unknown. Therefore, large-scale prospective studies are needed to establish the occurrence of autoimmune diseases in patients with a mesh implant.

In conclusion, 40 patients with a systemic illness, which developed after mesh implantation, are described in the study. It is postulated that the implanted mesh induced the systemic illness by enhancement of the innate and specific immunity in susceptible patients. We propose that prospective long-term follow-up studies have to be performed to evaluate whether patients with mesh implants develop ASIA, autoimmune diseases, and/or immunodeficiencies.

Practice points

- A systemic illness may develop after a PP mesh implantation
- Patients who develop this illness fulfill the diagnostic criteria for the "*autoinflammatory/autoimmunity syndrome induced by adjuvants*" (ASIA)
- In half of these patients, autoimmune diseases develop, whereas a quarter of the patients have an immunoglobulin G and/or immunoglobulin IgG subclass deficiency
- Patients with a pre-existing allergic disease are at increased risk for the development of ASIA after mesh implantation

Research agenda

- Establishment of validated questionnaires to evaluate the symptoms of "*autoinflammatory/autoimmunity syndrome induced by adjuvants*" (ASIA)
- Prospective studies after mesh implantation to determine the frequency of ASIA, autoimmune diseases, allergies, and/or immunodeficiency
- Epidemiologic studies to calculate the risk of ASIA, autoimmune diseases, allergies, and/or immunodeficiency after mesh implantation
- Animal studies in autoimmune-prone animals to study whether these animals have an increased susceptibility to and/or exacerbation of autoimmune disease after polypropylene mesh implantation
- Prospective randomized controlled studies to demonstrate the efficacy of doxycycline and/or other therapies in patients with mesh-induced ASIA.

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Conflicts of interest

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