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Review Article

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Tonsillectomy, appendectomy and splenectomy: sequels and malignant evolution

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Abstract

The excision of secondary lymphoid organs might not be harmless. Although the procedure itself, is less and less performed presently, infectious sequels in total splenectomy might occur and are possibly fatal. Among further complications, thromboembolic and immune alterations should also be expected. The most debatable of consequences, probably associated with an immune adjustment, concerns the development of malignancies. Considering post-splenectomy tumors, discrepancies emerge between their occurrence in humans, and their consequent protective effect in experimental animals. It is recommended that surgeons aspire at preserving as much of lymphoid tissues a feasible, when performing such resections.

Keywords: Tonsils, Appendix, Spleen, Consequence of Complete and Partial Resection, Cancer.

Introduction

In this narrative review, the consequences of the ablation of secondary lymphoid tissues are scrutinized. The excision is often carried out after traumatic injury (traumatic splenic rupture) but are sometimes performed to treat primary hematological diseases which are refractory to medical treatment (idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, or spherocytosis). Often, these resections follow chronic and acute inflammation (tonsillectomy) or hyperacute inflammation (appendectomy). The outcome of the above resections may be infectious, hematologic, immunologic, or neoplastic. Regarding some lymphoid organ ablations, the alterations in the microbiota might affect the far-reaching evolution into chronic immunologically associated diseases (inflammatory bowel diseases).

Consequences of Lymphoid Organ Resection

Splenectomy

Our analysis of this surgical procedure concerns mainly the complete ablation of the spleen, but it also includes its partial resection, which is being more widely adopted. Major post-splenectomy infectious diseases have frequently been reported. However, anti-meningococcal, anti-pneumococcal, and anti-Hemophilus influenzae vaccinations have markedly reduced the risk of sepsis and death. The indications for antibiotic prophylaxis are still uncertain and may depend on the patients' immune competence [1,2] and their genetic constitution. When evaluating the effects of splenectomy on vaccine immunogenicity, it seems that a near-total splenectomy represents the optimal condition for an adequate immunological reaction [3]. Mortality from splenectomy, occurring as a late sequel, is mainly due to sepsis, thromboembolic events, alcoholism (secondary to cirrhosis and trauma) and digestive disorders (peptic ulcers) [4]. In children, splenectomy is carried out for hereditary spherocytosis, Hodgkin lymphoma and severe idiopathic thrombocytopenic purpura. Overwhelming sepsis occurs in 3.8% of children and has a mortality rate of 2.5% [5]. Splenectomy might promote cancer. Thus, a population-based investigation, at national level in Taiwan has disclosed a higher incidence of gastrointestinal cancer, head and neck cancers, and malignant hematological tumors, predominantly in patients after non-traumatic splenic resections [6]. In Hodgkin lymphoma, secondary malignancies often include breast cancer following radiation with or without chemotherapy. In the 1970s, splenectomy was commonly performed as part of a staging laparotomy. The effects of splenectomy in Hodgkin lymphoma are independently associated with breast cancer occurrence [7].

In contrast, experimental splenectomy in mammary tumor-bearing rats leads to a markedly reduced tumor rate (45% in splenectomized rats compared with 70% in control rats). In tumor-carrying rats, splenectomy causes a significant increase in circulating NK cells. In these rats, the resected spleens contain fewer CD4+ and CD8+ lymphocytes and significantly more CD4- and CD8- lymphocytes [8]. A study in mice has further supported the role of splenectomy in inhibiting tumor growth and metastatic spread. The effect of splenectomy may be mediated by the depletion of myeloid suppressor cells [9]. Thus, splenectomy in a clinical context appears to produce a different, and permissive effect in promoting cancer, whereas in experimental animals it may suppress tumor growth. Of note, in the clinical setting, abnormal NK lymphocytes occur, following splenectomy and may be linked with recurrent infections, polyclonal B-cell proliferation and relapsing neutropenia [10]. In mice, however, resection of 70% of the spleen appears to be optimal, as it is accompanied by a marked decrease in mononuclear cells and prevents the marked leukocytosis related with complete ablation [11]. The immune response that occurs after a stroke, often delays neuronal death. In splenectomized rats, this neuroprotective effect is lost, due to mediation by IFN-γ [12]. Attempting to further clarify the multiple functions of the spleen, rats with cardiac allografts have undergone splenectomy. Splenectomy significantly extends the survival of the heart allograft by delaying inflammatory infiltrates and a subsequent myocardial rejection. Splenectomy also increases the lymphocytic apoptotic rate. In another paper, splenectomy was found to exert its effect by inducing immunological tolerance [13]. Myocardial ischemia-reperfusion injury shows that myocardial inflammation is localized in the re-perfused area. Splenectomy protects the myocardium by limiting the infiltration of the phagocytic monocytes [14]. In a cohort of 8,149 splenectomized veterans who were initially tumor-free, solid tumors (buccal, hepatic, colonic, esophageal, pancreatic, and pulmonary) have been found to be more frequent by a ratio of 1.3-1.9 compared with non-splenectomy individuals. In post-splenectomy veterans, hematological malignancies were more frequent by a ratio of 1.8-6.0 compared with non-splenectomy individuals. Death from any cancer in this group of patients was from1.3 to 4.7 times more frequent than in individuals with an intact spleen [15]. The above findings may be consistent with the post-splenectomy cancer progression in rats and mice, as described many years ago [16,17]. Any discrepancies in the epidemiologic reports may be due to the inclusion of patients who had developed cancer before splenectomy [15].

Spleen preservation procedures, including non-surgical management, and the atrial embolization of a laceration, have, to a large extent replaced total splenectomy. Currently, 90% of splenic tears are treated medically.

Tonsillectomy and adenoidectomy

In humans, the pharyngeal tonsils and the palatine tonsils represent the main mass of the Waldeyer's ring. In these tissues, the intraepithelial and subepithelial lymphoid cells give rise to both local and systemic immunological reactions. However, it seems that, in children a Th1 cellular response is predominant in the pharyngeal tonsils, whereas a Th2 humoral immune reaction prevails in the adenoids [18]. Total tonsillectomy is performed less frequently than in the past in most medical centers. The indications for this procedure are limited to medically resistant tonsillitis and suspected malignancy. In most these cases, the sublingual tonsil is not damaged. It appears that the incidence of oropharyngeal carcinoma, mainly the HIV-related type, is increasing worldwide. Tonsillectomy decreased the risk of tonsil carcinoma to a significant degree [19].

In Taiwan, however, a national inquiry found a significantly increased risk of developing cancer after tonsillectomy, at a rate of 4.28 per 1,000 person-years, compared with 2.9 per 1,000 person years in non-tonsillectomy controls. No site-specific association with any given type of malignancy has been found, except for a nearly significant link with breast cancer at 3 years or more after tonsillectomy [20]. A cohort of 215 patients was identified, who had developed gallstones and had undergone cholecystectomy or tonsillectomy. An association between gallstones, the surgical procedures and pancreatic cancer was displayed. Although having gallstones and undergoing a cholecystectomy significantly increased the risk of pancreatic cancer, a tonsillectomy reduces the tendency to this cancer [21]. Finding an incidental cancer during a routine tonsillectomy occurs very rarely (11 cases in 72,322 procedures). This does not justify performing routine tonsillectomies on clinically benign tonsils [22]. The association between tonsillitis, tonsillectomy and Hodgkin lymphoma was examined in all Danish residents between 1977 and 2001. Hodgkin lymphoma was diagnosed in 2,988 residents. Of these, 58 had undergone tonsillectomy after tonsillitis, and 14 had suffered exclusively from tonsillitis. The findings suggest that tonsillitis is a risk factor for Hodgkin lymphoma, irrespective of the age of the patient [23]. The reports linking a greater incidence of Hodgkin lymphoma after tonsillectomy have shown some inconsistencies. Of note, the age at tonsillectomy had varied. Irrespective of the immune functions of the tonsil and their modulation during growth, a marked risk of Hodgkin lymphoma prevails in cases of tonsillectomy prior to age 12. However, this risk is substantially decreased if the ablation occurs at an older age [24]. Tonsillectomy and adenoidectomy, if performed in an adult, the risk of lymphocytic leukemia, but not of myeloid leukemia is increased markedly. The cutoff point for these procedures is at 10 years of age [25]. Eighty children were submitted to tonsillectomy for chronic tonsillitis. No change was observed in serum immunoglobulins after the procedure. The subjects' preoperative peripheral lymphocyte count was higher than in the control group. It was restored to normal after surgery. Following tonsillectomy PPD and Candida tests had improved. In children with adenoid hypertrophy and chronic tonsillitis, the immune response analysis showed increased levels of CD19+ and CD23+ B lymphocytes before resection. Following ablation, B-lymphocyte activation was normalized. A compensatory reaction did occur, but no immune deficiency developed.

Appendectomy

It has been suggested that the resection of lymphoid tissue, such as occurs with appendectomy at an early age, may increase the risk of cancer. This hypothesis has been explored in a large series of children undergoing appendectomy in Sweden between 1965 and 1993. No increased overall risk of cancer was found. However, a significant increased incidence of gastric cancer was noted (SIR: 2.45), as well as a marginal increased incidence of non-Hodgkin lymphoma (SIR: 1.55). These malignancies developed 15 years or more after appendectomy [26].

Recently, non-surgical treatment of an appendix mass has been suggested as the preferred means of treatment, followed in some cases, by an interval appendectomy. Inconsistent results were disclosed in three retrospective pediatric studies of non-surgical treatment. The risk of recurrent appendicitis reached 20%. The complication rate of interval appendectomy (IA) was 3.4% and the incidence of carcinoid tumor at IA was 0.9%. But no comparison between routine IA and non-surgical treatment without IA was available. In adults, IA may be performed to establish the etiology of the perforation, but the significance of IA after non-surgical treatment of perforated appendicitis is still uncertain. In a further study, a tumor was diagnosed in 14 patients (3.7%). Five of these patients had been submitted to IA (29.4%). Nine tumors were mucinous and the patient with neoplasia were older than 40 years [27]. The proclivity for cancer after appendectomy for appendicitis has remained obscure. The risk of cancer decreased from 13.7 in the first three months following appendectomy, to 1.37 at 7-12 months thereafter. It has been suggested that a high incidence of cancer soon after an appendectomy might signify that acute appendicitis may reveal that acute appendicitis may be an early sign of remote malignancies [28]. But no consensus thereof was reached.

Inflammatory bowel diseases are most probably chronic immune mediated conditions. In addition to a response to dysregulated commensal microbes, several external factors are relevant to these diseases in genetically prone subjects. In these exposed individuals, appendectomy has been noted, regarding the etiology of IBD. But the role of this procedure in IBD is debatable, being considered as potentially reducing the risk of ulcerative colitis only (OR, 0.29), while others did not demonstrate an effect on IBD [29].

Discussion

Complete resection of the spleen, tonsils and appendix is related to complications which are infectious, vascular, and immunologic. The most intriguing consequences, however, but also the more debatable, are those connected with the evolution of malignant tumors. Post-splenectomy pneumococcal and meningococcal septicemia should be rare, pending the availability for vaccination. In humans, splenectomy may cause polyclonal B-cell lymphocytosis, abnormal NK lymphocytosis and recurrent neutropenia. In contrast, in mice, splenectomy may produce excessive leukocytosis and impede allograph rejection.

Splenectomy in humans might promote carcinogenesis. Solid tumors, including hepatic, colonic, prostatic, pancreatic, and pulmonary are the most frequent. It has been suggested that the contradictions evoked among some epidemiologic views regarding the absence of cancer after splenectomy, may be due to the inclusion of malignant tumors present before the resection. The post-resection propensity for cancer, regarding the tonsils, and to a lesser extent the appendix, is weaker, but, nevertheless evident. In experimental animals, splenectomy may suppress tumorigenesis, highlighting the basic difference between spontaneous malignancies in human, and viral-induced tumors in the laboratory models.

The surgical specialties have adapted the relevant surgeries, in such a way, that most or part of these secondary lymphoid organs are spared (subtotal tonsillectomy in sleep apnea syndrome), thereby protecting their immune function and possibly impeding cancer.

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