Clinics in Oncology

Case Report
Published: 21 Jul, 2016

Splenectomy Tonsillectomy and Appendectomy - Complications and Cancer Occurrence

Benharroch D[1]*, Nalbandyan K[1], Kraus M[2], Osyntsov A[3] and Ariad S[4]

[1]Department of Pathology, Soroka University Medical Center and the Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva, Israel

[2]Department of ENT, Soroka University Medical Center and the Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva, Israel

[3]Department of Surgery B, Soroka University Medical Center and the Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva, Israel

[4]Department of Oncology, Soroka University Medical Center and the Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva, Israel

Abstract

The removal of secondary lymphoid tissue is not innocuous. Infectious complications in procedures such as total splenectomies are frequent and may be fatal. Sequelae may be thromboembolic. Immune alterations are expected after such procedures. The most controversial consequence, one that is linked with immune changes, is the development of malignant tumors. Regarding post-splenectomy malignancies, there appears to be marked discrepancies between the increased occurrence of tumors in humans and the protective effects seen in experimental animals. It is recommended, that surgeons strive to preserve as much lymphoid tissue as possible.

Introduction

In this review, the effects of the resection of secondary lymphoid organs are evaluated. These excisions are often performed after traumatic injury (traumatic splenic rupture), but are sometimes performed to treat primary hematological diseases that 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 consequences of any of the above resections may be infectious, hematological, immunological or neoplastic. For some lymphoid organ resections, the changes in the microbiota may be responsible for the far-reaching development of chronic immunologically associated diseases (inflammatory bowel diseases).

Consequences of Lymphoid Organ Resection

Splenectomy

Our discussion of this surgical procedure mainly concerns the complete ablation of the spleen, but it also includes partial resection, which will probably be widely adopted in the future. Major post-splenectomy infections have frequently been described. 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 probably depend on patients' immune competence [1,2] and their genetic predisposition. When considering the effects of splenectomy on vaccine immunogenicity, it appears that a near-total splenectomy represents the optimal condition for an adequate immunological reaction [3]. Mortality from splenectomy, occurring as a late complication, is mainly due to sepsis, thromboembolic events, alcoholism (due to the risk of cirrhosis and trauma) and digestive disorders (peptic ulcers) [4]. In children, splenectomy is performed 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 may promote cancer. Indeed, a population-based investigation conducted at the national level in Taiwan has found a higher incidence of gastrointestinal cancer, head and neck cancers, and hematological malignant tumors, specifically in patients who had undergone non-traumatic splenic resection [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

OPEN ACCESS

Correspondence:
Daniel Benharroch, Department of Pathology, Soroka University Medical Center, 1, ItshakRagerBoulv, P.O.Box 151, Beer-Sheva 84101, Israel. Tel: +972-507579140; E-mail: danielbenharroch1@gmail.com

Received Date: *30 Jun 2016*
Accepted Date: *17 Jul 2016*
Published Date: *21 Jul 2016*

Citation:
Benharroch D, Nalbandyan K, Kraus M, Osyntsov A, Ariad S. Splenectomy Tonsillectomy and Appendectomy - Complications and Cancer Occurrence. Clin Oncol. 2016; 1: 1037.

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 effects 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. Notably, in the clinical setting, abnormal natural killer lymphocytes is follows splenectomy and may be associated with recurrent infections, polyclonal B-cell proliferation and relapsing neutropenia [10]. In mice, however, resection of 70% of the spleen appears to be optimal because this amount is accompanied by a marked decrease in mononuclear cells and prevents the excessive leukocytes is observed in a complete resection [11].The immune response that occurs after a stroke often delays neuronal death. In splenectomized rats this neuroprotective effect is lost as it is mediated by IFNγ [12].

In an attempt to further clarify the multiple functions of the spleen, rats with cardiac allografts have been splenectomized. Splenectomy significantly extends the survival of the heart allograft by delaying inflammatory infiltrates and subsequent myocardial rejection. Splenectomy also increases the lymphocytic apoptotic rate. In another study, splenectomy has been found to exert its effects 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 phagocytic monocytes [14]. In a cohort of 8,149 splenectomized veterans who were initially tumor-free, solid tumors (buccal, hepatic, colonic, esophageal, pancreatic, prostatic and pulmonary) have been found to be more frequent by a ratio of 1.3-1.9, compared with non-splenectomized individuals. In the splenectomized veterans, hematological malignancies were more frequent by a ratio of 1.8-6.0 compared with non-splenectomized individuals. Death from any cancer in this group of patients was from 1.3 to 4.7 times more frequent than in the non-splenectomized group [15]. The findings of this study, although supported by only few epidemiological reports, may be consistent with the experimental results of post-splenectomy cancer progression in mice and rats as described many years ago [16,17]. These discrepancies in the epidemiological reports may be due to the inclusion of patients who had cancer prior to splenectomy in some of the studies [15].

Spleen preservation procedures, including non-surgical management and the arterial 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 tonsil 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 adenoid [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 or suspected malignancy. In the majority of these cases, the sublingual tonsil is not damaged. It appears that the incidence of or opharyngeal carcinoma, mainly the HIV-related type, is increasing worldwide. In a large study from Denmark, no association between tonsillectomy and oropharyngeal carcinoma or other malignant tumors has been found. However, tonsillectomy decreased the risk of tonsil carcinoma to a significant degree [19].

In Taiwan, in contrast, a national study has found a significantly increased risk of developing cancer after a tonsillectomy at a rate of 4.28 per 1,000 person-years compared with 2.9 per 1,000 person-years in non-tonsillectomized controls. No site-specific association with any particular type of cancer has been found, except for a nearly significant link with breast cancer at 3 years or more after the 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 apparent. Although having gallstones and undergoing a cholecystectomy significantly increases the risk of pancreatic cancer, a tonsillectomy reduces the tendency to develop this cancer [21]. Finding an incidental cancer during a routine tonsillectomy occurs very rarely (11 cases in 72,322 procedures [0.015%]). This finding does not justify performing a routine tonsillectomy on clinically benign tonsils [22]. The associations among 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 residents had undergone tonsillectomy after tonsillitis, and 14 suffered from tonsillitis only. These results 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. The age at tonsillectomy has especially varied. Irrespective of the tonsil immune functions and their alterations during growth, a marked risk of Hodgkin lymphoma has been found in patients who had undergone tonsillectomy before age twelve. However, this risk is substantially decreased if the resection was performed at an older age [24]. However, when a tonsillectomy and an adenoidectomy were performed an older age the risk of adult lymphocytic leukemia, but not of myeloid leukemia, is markedly augmented. The cutoff point for performing these surgeries was at 10 years of age [25]. An immunological in vestigation was conducted in 80 children who had undergone tonsillectomy for chronic tonsillitis. In this study, no change in serum immunoglobulins was found after surgery. The subjects' pre-operative peripheral lymphocyte count was higher than that of the controls, but was restored to near normal after surgery. Improved cell-mediated skin tests with PPD and Candida were observed after tonsillectomy.The immune response at 24-48 hours before and at 4-6 weeks after an adenotonsillectomy has been analyzed in children with adenoid hypertrophy and chronic tonsillitis. Increased levels of CD19+ and CD23+ B-lymphocytes were found before resection. After ablation, B-lymphocyte activation was normalized, CD8+ T-lymphocyte levels were increased, and mild reductions in IgG, IgA and IgM were noted. A compensatory reaction had occurred but no immune deficiency was found.

Appendectomy

It has been hypothesized that the resection of lymphoid tissue, such as occurs in appendectomy at an early age, may increase the risk

of cancer. This hypothesis has been investigated in a large series of children who had undergone appendectomies 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 cancers occurred at 15 years or more after the appendectomy [26].

Recently, non-surgical treatment of an appendix mass has been suggested as the preferred course of treatment management, followed by an interval appendectomy in some cases. In three retrospective pediatric studies of non-surgical treatment, inconsistent results have been found. The risk of recurrent appendicitis was as high as 20%. The complication rate of interval appendectomy (IA) was 3.4% and the incidence of carcinoid tumor disclosed at IA was 0.9%. However, 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 the role of IA after non-surgical treatment of perforated appendicitis is still uncertain. In one study, a tumor was diagnosed in 14 patients (3.7%), and five of these patients had undergone IA (29.4%). Nine tumors were mucinous (64.3%). The patients with neoplasia were older than forty years [27]. The development of cancer after appendectomy for appendicitis has remained unclear. A study from Taiwan has examined the role of appendicitis in indicating a distant tumor. A cancer incidence was 4.64 times more frequent in the appendicitis group of patients compared with the control group. The tumors were mainly of the digestive tract and the female genital system. The risk of cancer decreased from 13.7 in the first 3 months after appendectomy to 1.37 at 7-12 months after appendectomy. It has been suggested that the high incidence of cancer soon after an appendectomy may signify that acute appendicitis is an early sign of remote malignant tumors [28]. However, a consensus has not been reached regarding this conclusion. Crohn's disease and ulcerative colitis are related inflammatory bowel diseases (IBDs) that are most probably chronic immune mediated conditions. In addition to a response to dysregulated commensal microbes, several external factors are pertinent to the development of these diseases in genetically vulnerable subjects. Among these exposed individuals, appendectomy has been mentioned in the etiology of IBD. However, the role of appendectomy in IBD is controversial, and appendectomy has been considered to reduce the risk of ulcerative colitis only (OR, 0.29); no effect on the incidence of IBD has been demonstrated by others [29]. Tonsillectomy has been shown to increase the risk of Crohn's disease, although this is probably an unrelated effect.

Discussion

Complete resections of the spleen, tonsils and appendix are related with sequelae that are infectious, vascular and immunologic. The most intriguing consequences, however, but also the most controversial, are those linked to the occurrence of malignant tumors. Post-splenectomy pneumococcal or meningococcal septicemia should be rare wherever vaccination is available. 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 allograft rejection. Splenectomy in humans may promote carcinogenesis. Solid tumors including hepatic, colonic, prostatic, pancreatic and pulmonary are the most frequent. It has been suggested that the inconsistencies among some epidemiological studies that show no propensity for cancer after splenectomy may be due to the inclusion of patients with malignant tumors that were present before the resection. With regard to the tonsils and to a lesser extent the appendix, the post-resection tendency for carcinogenesis is weaker but nonetheless evident. In experimental animals splenectomy may suppress tumorigenesis, thus emphasizing a further basic difference between spontaneous malignancies in humans and viral-induced tumors in the laboratory models.

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

Acknowledgements

No contribution was necessary for the preparation of this manuscript.

References

1. Altamura M, Caradona L, Amati L. Splenectomy and sepsis: the role of the spleen in the immune mediated bacterial clearance. Immunopharmacol Immunotoxicol. 2001; 23: 153-161.
2. Kaplinsky C, Spirer Z. Post-splenectomy antibiotic prophylaxis, an unfinished story: to treat or not to treat? Pediatr Blood Cancer. 2006; 47: 740-741.
3. Stoehr GA, Luecken J, Zielen S. Mode of splenectomy and immunogenicity of meningococcal vaccination in patients with hereditary spherocytosis. Br J Surg. 2008; 95: 466-471.
4. Linet MS, Nyren O, Gridley G. Causes of death among patients surviving at least one year following splenectomy. Am J Surg. 1996; 172: 320-323.
5. Meekes I, van der Staak F, van Oostrom C. Results of splenectomy performed in a group of 91 children. Eur J Pediatr Surg. 1995; 5: 19-22.
6. Sun LM, Chen HJ, Jeng LB. Splenectomy and increased subsequent cancer risk: a nationwide population-based cohort study. Am J Surg. 2015; 210: 243-251.
7. Chung CT, Bogart JA, Adams JF. Increased risk of breast cancer in splenectomized patients undergoing radiation therapy for Hodgkin's disease. Int J Radiat Oncol Biol Phys. 1997; 37: 405-409.
8. Kossoy G, Ben-Hur H, Lifschitz O, Zusman I. Mammary tumors in splenectomized rats. Oncol Rep. 2002; 9: 185-188.
9. Levy L, Mishalian I, Bayuch R. Splenectomy inhibits non-small cell lung cancer growth by modulating anti-tumor adaptive and innate immune response. Oncoimmunology. 2015; 4: e998469.
10. Granjo E, Lima M, Fraga M. Abnormal NK-cell lymphocytosis detected after splenectomy: association with repeated infections, relapsing neutropenia and persistent polyclonal B-cell proliferation. Int J Hematol. 2002; 75: 484-488.
11. Bessler H, Bergman M, Salman H. The relationship between partial splenectomy and peripheral leukocyte count. J Surg Res. 2004; 122: 49-53.
12. Seifert HA, Leonardo CC, Hall AA. The spleen contributes to stroke-induced neurodegeneration through interferon-gamma signalling. Metab Brain Dis. 2012; 27: 131-141.
13. Zhu J, Chen S, Wang J. Splenectomy increases the survival time of heart allograft via developping immune tolerance. J Cardiothorac Surg. 2013; 8: 129.
14. Goltz D, Huss S, Ramadori E. Immunomodulation by splenectomy or by FTY720 protects the heart against ischemia-reperfusion injury. Clin Exp Pharmacol Physiol. 2015; 42: 1168-1177.
15. Kristinsson SY, Gridley G, Hoover RN. Long term risks after splenectomy among 8,149 cancer-free American veterans: a cohort with up to 27 years follow-up. Hematologica. 2014; 99: 392-398.

16. Hull CC, Galloway P, Gordon N. Splenectomy and the induction of murine colon cancer. Arch Surg. 1988; 123: 462-464.

17. Yamagishi H, Pellis NR, Kahan BD. Effect of splenectomy upon tumor growth: characterization of splenic tumor-enhancing cells *in vivo*. Surgery. 1980; 87: 655-661.

18. Komorowska A, Komorowski J, Banasik M. Cytokines locally produced by lymphocytes removed from the hypertrophic nasopharyngeal and palatine tonsils. Int J Pediatr Otorhinolaryngol. 2005; 69: 937-941.

19. Fakhry C, Andersen KK, Christensen J. The impact of tonsillectomy upon the risk of oropharyngeal carcinoma diagnosis in the Danish Cancer Registry. Cancer Prev Res (Phila). 2015; 8: 583-589.

20. Sun LM, Chen HJ, Li TC, Sung FC, Kao CH. A nationwide population-based cohort study on tonsillectomy and subsequent cancer incidence. Laryngoscope. 2015; 125: 134-139.

21. Zhang J, Prizment AE, Dhakal IB, Anderson KE. Cholecystectomy, gallstones, tonsillectomy and pancreatic cancer: a population-based case control study in Minnesota. Br J Cancer. 2014; 110: 2348-23453.

22. Rokkjaer MS, Klug TE. Malignancy in routine tonsillectomy specimens: a systematic literature review. Eur Arch Otorhinolaryngol. 2014; 271: 2851-2861.

23. Vestergaard H, Westergaard T, Wohlfahrt J, Hjalgrim H, Melbye M. Tonsillitis, tonsilectomy and Hodgkin's lymphoma. Int J Cancer. 2010; 127: 633-637.

24. Vineis P, Miligi L, Crosignani P. Delayed infection, late tonsillectomy or adenoidectomy and adult leukemia: a case-control study. Br J Cancer. 2003; 88: 47-49.

25. Liaw KL, Amadi J, Gridley G, Nyren O, Linet MS. Risk of Hodgkin's disease subsequent to tonsillectomy: a population-based study in Sweden. Int J Cancer. 1997; 72: 711-713.

26. Cope JU, Askling J, Gridley G. Appendectomy during childhood and adolescence and the subsequent risk of cancer in Sweden. Pediatrics. 2003; 111: 1343-350.

27. Furman MJ, Cahan M, Cohen P, Lambert LA. Increased risk of mucinous neoplasms of the appendix in adults undergoing interval appendectomy. JAMA Surg. 2013; 148:703-706.

28. Wu SC, Chen WT, Muo CH, Sung FC. Appendicitis as an early manifestation of subsequent malignancy: an Asian population study. PLoS One. 2015; 10: e0122725.

29. Hansen TS, Jess T, Vind I. Environmental factors of inflammatory bowel disease: a case control study based on a Danish inception cohort. J Crohns Colitis. 2011; 5: 577-584.