**ReseaRch PeRsPective**

**Inflammation-Infection: A Complication or Trigger of Lymphedema**

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Lymphedema remains a prevalent and potentially debilitating chronic condition affecting more than 3 million people in the United States with the majority of cases related to cancer treatment (Lawenda, Mondry, & Johnstone, 2009). Lymphedema negatively affects individuals’ social, emotional, functional, and financial lives (Pyszel et al., 2006; Shih et al., 2009). Lymphedema secondary to cancer treatment, also known as acquired lymphedema, is characterized by an accumulation of lymph fluid in the interstitial spaces of the affected limb and adjacent areas, leading to a syndrome of abnormal swelling and multiple distressing symptoms, including heaviness, tightness, firmness, pain, numbness, stiffness, or impaired limb mobility (Paskett et al., 2007; Fu, & Rosedale, 2009).

Cellulitis (also called acute inflammatory episode) is a serious, costly, and very occasionally life-threatening complication of lymphedema. Repeated cellulitis, infections and lymphangitis have been reported in persons with lymphedema (Shih et al., 2009; Weissleder & Schuchhardt, 2001). Individuals with lymphedema are often cautioned to avoid punctures or other trauma to the limbs to decrease their infection risk. However, even without trauma, sudden onset of redness, warmth, increased swelling, and tenderness in the swollen limb/areas are not uncommon (Weissleder & Schuchhardt, 2001). Early research focused on infection, specifically cellulitis and lymphangitis, as a complication from lymphedema (Brorson & Svensson, 1997; Filippetti et al., 1994; Pillar & Thelander, 1998). In a study of liposuction as a treatment for lymphedema in arms of breast cancer survivors, Brorson and Svensson (1997) followed limb size, skin blood flow, and cellulitis in 12 subjects for 12 months. All participants had swollen arms, decreased skin blood flow, and cellulitis as symptoms prior to surgery. Following liposuction the researchers reported clinical improvement in limb size, skin blood flow, and cellulitis. Lack of information related to duration or grade of lymphedema makes it difficult to determine if cellulitis or skin blood flow problems occur more frequently the longer an individual has the condition or if they are equally likely to occur in all stages and over all time intervals. Pillar and Thelander included in their 1998 low level laser study an infection risk index. All ten women in this study were evaluated pretreatment and posttreatment. Skin integrity and disfigurement were measured. Prior to treatment all subjects were at risk. During the first four weeks of treatment the index increased. Only moderate improvement in the index was noted at the end of treatment and for six months after treatment the index continued to decline. 2.5 years after treatment the infection risk index had returned to near pretreatment levels in all participants despite continued reduction in pretreatment limb size. This finding suggests that actual limb size may not correlate with infection risk and that this risk may be omni-present in this population.

Recent research on lymphedema secondary to cancer treatment reveals that inflammation-infection or injuries are among predictive risk factors for developing lymphedema following breast cancer treatment (Goffman et al., 2004; Mak et al., 2008; Soran et al., 2006; Tsai et al., 2009). A recent prospective study of 936 breast cancer survivors has revealed that infection or injuries are the main risk factors for lymphedema (Mak et al., 2008; Mclaughlin et al., 2009). A matched case-control study of 202 breast cancer survivors has showed that women who had previous inflammation-infection in the breast, chest, or arm were 3.80 times more likely to develop lymphedema (Mak et al., 2008). Breast cancer survivors who underwent surgery and dissection of lymph nodes and vessels are known to have a compromised lymphatic system which makes them more vulnerable to ineffective lymphatic drainage and inflammation-infection. Inflammation-infection worsens ineffective lymphatic drainage by bringing more fluid to the affected areas as part of the normal body response to inflammation-infection. Accumulated fluid triggers lymphangiogenesis as an attempt to remove the excess fluid (Angelii et al., 2006; Scavelli et al., 2004). Fluid continues to accumulate on a daily basis. This fluid is an ideal medium for bacteria that leads to more inflammation and creation of additional lymphatic vessels that may not effectively remove the excessive fluid, leading to lymphedema. Because sustained inflammation is not resolved, more fluid accumulates with creation of new lymphatic vessels. Such an inflammation-driven lymphangiogenesis maintains the inflammation further damaging the lymphatic system leading to lymphedema (Scavelli et al., 2004; Stanton et al., 2009; Thaunat et al., 2006).

In summary, previous and recent research on patients with lymphedema and those at risk show that localized Infection-
inflammation in the affected limb, regardless of whether it is induced by cancer surgery or radiation therapy, or minor injuries (scratches or burns) is a complication as well as a trigger of lymphedema. The role of inflammation in lymphedema pathogenesis provides insights into the dual consequences of localized infection-inflammation in patients who develop lymphedema secondary to cancer treatment (Angeli et al., 2006; Collado-Hidalgo et al., 2008; Scavelli et al., 2004; Stanton et al., 2009). Recent research suggests that chemotherapy may be an important risk factor for lymphedema (Norman et al., 2010). It remains unclear whether chemotherapy plays a role in inducing or promoting inflammation-infection in patients who are at risk for lymphedema. It also remains unclear if genetic predisposition may also place a patient at higher risk of lymphedema. Future research should focus on genotypic and molecular mechanism of infection-inflammation as a trigger or complication of lymphedema.

References


