Lymphology 49 (2016) 185-191

LYMPHSPIRATION

THE AXILLARY WEB AND ITS LYMPHATIC ORIGIN

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ABSTRACT

Axillary web syndrome (AWS) is a frequently overlooked problem that causes morbidity in the early post-operative period following cancer surgery with axillary lymph node removal (1-3). AWS, also known as "cording" was first described in 2001 by Moskovitz as "a visible web of axillary skin overlying palpable cords of tissue that are made taut by shoulder abduction" (1). Over a decade has passed since Moskovitz's seminal article was published, and we still lack a good understanding of AWS. This condition has been suboptimally studied using widely differing criteria. This has resulted in almost meaningless data such as the incidence of the problem, which varies from 6 to 72% following cancer surgery with axillary lymph node dissection (ALND) or sentinel node biopsy (SNB) (1-5). AWS continues to perplex the medical and scientific community. For instance, there is no explanation for the observation that individuals with a lower body mass index (BMI) are at higher risk for AWS (1-3). There are differing views on the physiological and etiological aspects of AWS. Some believe there is a vascular component involving the lymphatic and/or venous system (1, 6-11). Others consider the cord to be composed of fascial tissue (12). The terminology used to describe the cord varies dependent on the researcher's opinions, which are based on their speculations as to the underlying pathophysiology of the condition.

The purpose of this paper is to present a new perspective that supports the theory that AWS is associated with the lymphatic system. Based on our clinical experience including more in-depth analysis of specific cases, our clinical research, and the accumulated literature, we present our proposal to explain the pathophysiology of AWS, define the period of onset and duration of AWS, outline possible reasons for the association between AWS and BMI, and postulate why we occasionally see cases of AWS that are associated with conditions that disturb normal lymphatic function but are unrelated to surgery.

Keywords: axillary web syndrome, cording, lymphatic function, lymphatic endothelium, D2-40

AWS Following Cancer Surgery

AWS most often occurs in the early post-operative period following surgical axillary lymph node removal for cancer (1,3,5,13). Early literature suggested that AWS resolved on its own by 3 months (1,2). More recent literature reports that cords can persist for more than 3 months (3). A higher BMI is associated with a lower risk of developing AWS for unknown reasons (2,3,14).

The early onset of AWS following

surgery coincides most commonly with the second phase of post-operative healing. When tissue injury occurs, 3 phases of healing follow, which have been commonly labeled the inflammatory, proliferative, and maturation phases (15). The inflammatory phase initiates a cascade of events including an increase in lymphatic flow that mobilizes the excess fluid and proteins caused by inflammation (16). The usual onset of AWS occurs about 2 to 4 weeks after surgery during the proliferative phase of healing (1). During the proliferative phase, new blood vessels develop (angiogenesis), fibroblasts produce collagen, and extracellular matrix is formed (15).

Our hypothesis is that AWS is an excessive but otherwise normal lymphatic phenomenon related to the body's natural healing process. During surgery that involves axillary lymph node removal, the lymphatic system is disrupted in discrete focal areas. In some places, it is completely interrupted or obstructed by sutures or cautery (17). In other places, it is disrupted so that it leaks into the surrounding tissue (18,19). This combination of injuries leads to focal areas of lymphatic obstruction or even backflow and leakage of lymphatic fluid into the interstitial tissue through both iatrogenic leaks and through the walls of obstructed and distended vessels. The body responds to this lymphatic injury by attempting to reestablish lymphatic flow and remove lymphatic fluid from the interstitial space (15). Because the injury is surgical, there is only a minimal amount that can be accomplished by lymph vessel recanalization. However, disrupted vessels will tend to reconnect, existing bypassing lymphatic collaterals will enlarge, and new lymphatic connections will form between existing lymph vessels (lymphangiogenesis). The high protein content lymphatic fluid that leaks from sites of vessel disruption tends to form small to microscopic lymphoceles. The fluid that leaks out of high pressure congested or inflamed vessels into the interstitial tissue, tends to concentrate around the lymphatic vessels. Lymphatic fluid is normally hypocoagulable (20). However, when the extravasated fluid is exposed to extravascular tissue and cellular factors, it contains enough clotting elements to coagulate (20). We propose that this protein-containing fluid can result in a fibrotic "tethering" of the vessel to the surrounding subcutaneous tissue. We then hypothesize that the taut cords seen in AWS are caused by the combination of a pathophysiological process that is based on the progressive retraction of the tethered tissue caused by the peri-lymphatic "clot" as it matures and retracts, and this retraction and tethering becomes clinically evident as a tightening of the linear bands by the act of abducting the arm.

The speed with which cords resolve differs among individuals. Earlier literature reported that the cords resolved by 3 months following surgery (1,2). In a recent study, however, 59% of individuals still exhibited cording 3 months after surgery (3). Another study also reported the presence of AWS beyond 3 months suggesting AWS may last for years or never completely resolve (3,5). We hypothesize that the resolution of the cords could be explained by the eventual formation of adequate lymphatic collateral pathways such that further leakage is avoided and the clotted fluid is absorbed. Chronic persistence of cording could be related to an unsuccessful development of adequate lymphatic collateral connections with persistent high pressure leakage. This could be due to the severity of the surgical injury or genetic or developmental causes of a reduced capability for lymphangiogenesis. Delayed development of AWS may be due to a less severe surgical injury; or genetic or developmental factors that result in either lower volume or lower pressure lymphatic flow in the extremity; or easier and faster development of spontaneous collaterals that then become insufficient over time.

Individuals with a higher BMI are at lower risk for AWS development (2,3,14).

It has been theorized that AWS may actually be present in patients with a higher BMI but that the cords cannot be detected inside or under the excess adipose tissue (2). Decreased detectability could be due to the fact that the cords are less visible or are less easily palpated or both. It has also been suggested that a thick layer of subcutaneous adipose tissue may prevent adhesions during the early phase of scar formation (2).

We hypothesize that AWS might not be seen in subjects with a higher BMI because the excessive adipose tissue may not allow the changes to occur that would lead to cording. Obesity predisposes individuals to various blood vascular and lymphatic abnormalities. Some of these abnormalities result in poor wound healing (21). One factor implicated in poor healing is the reduced microvascularity in the subcutaneous, fat-laden tissue of obese individuals (22). The vascularity changes lead to reduced nutrition and oxygen in the tissue, which can delay healing. Adipose tissue secretes bioactive substances, such as adipokines, which may also negatively influence the healing process (23,24). Other abnormalities associated with obesity adversely affect the lymphatic system and result in abnormal lymphatic architecture, decreased density of capillary lymphatics, and functional impairment of lymphatic vasculature (25,26). These changes in the lymphatic system may affect paracrine signaling, which could inhibit lymphangiogenic growth factors. We hypothesize that excessive subcutaneous fat leads to smaller, less linear lymphatic vessels, which reduces the amount of subcutaneous localized leakage and clotting. This may also inhibit or suppress lymphangiogenic growth factors impeding the reestablishment of lymphatic flow through lymphangiogenesis or collateral pathways. This could help explain why subjects with a high BMI are at higher risk for lymphedema development but at lower risk of AWS.

Cases of AWS Unrelated to Surgery

Much of the literature on AWS relates to surgical removal of lymph nodes due to surgery for breast cancer or melanoma. From clinical experience and the literature, we have seen that AWS sometimes occurs without surgery. It has been associated with metastatic cancer, infection, and strenuous exercise. Though the presence of cording in these cases is unrelated to surgical injury to the lymphatic system, the development of the cords appears to be associated with a disturbance in normal lymphatic function.

Moskovitz first described a patient who developed AWS prior to surgery who had Stage 4 breast cancer with metastatic disease to the axillary lymph nodes (1). The primary author of this paper (LK) experienced two similar cases, one of a woman with Stage 4 breast cancer who developed AWS prior to surgery; and the other of a woman who was referred to physical therapy for AWS prior to her breast cancer surgery with known lymph node involvement. This raises the possibility that AWS could be an indicator of cancer metastasis in the lymph nodes. We speculate that AWS prior to surgery could be related to an accumulation of cancer cells in the lymph nodes or lymphatic vessels leading to high pressure congestion in the lymphatics and the same type of perivascular lymphatic leaking and clotting as described above for the post-operative patients.

Biopsies of AWS cords that occurred in circumstances unrelated to surgery provide histopathological evidence for lymphatic involvement. Rashtak et al reported a case of AWS associated with an infection. A male patient developed AWS following the onset of a furuncle in the ipsilateral axilla (27). Histopathology of the cord demonstrated a lymphatic vessel and positive staining for D2-40, a marker for lymphatic endothelium (27). Further support of lymphatic involvement has been demonstrated by a case of cording in the neck of a carpenter who carried heavy loads on his shoulder on the same side as the cord (28). Though this article referred to the cord as Mondor's disease, the presentation

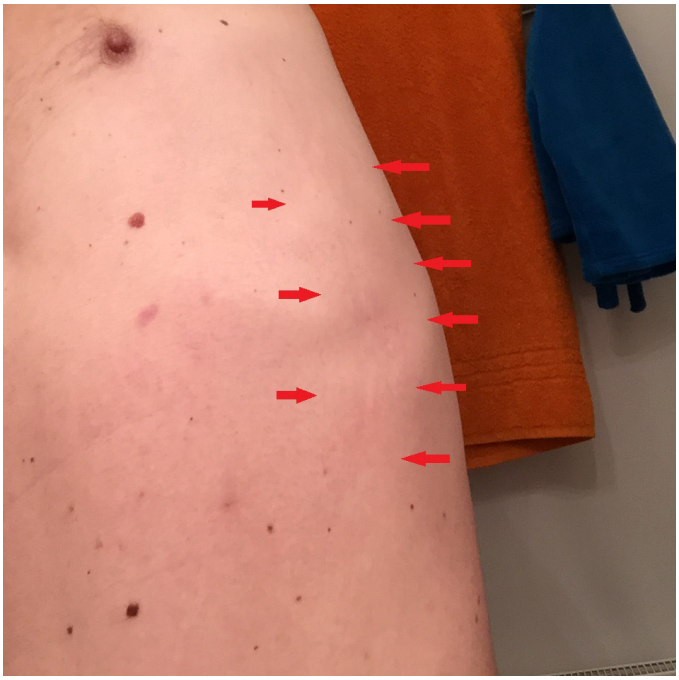

Fig. 1. Photograph highlighting (arrows) the cord-like structure on left chest at 2-3 month post first appearance.

was analogous to AWS. The cord stained positive for D2-40 providing immunohistochemical evidence that the cord was lymphatic in origin.

Through correspondence and personal experience, the primary author (LK), is aware that AWS can appear in some individuals following strenuous exercise, which to our knowledge, has never been reported in the literature. In correspondence with a healthy 30-year old woman with a normal BMI (19kg/m^2), the clinical picture, which was not verified with a physical exam, was strongly suggestive of AWS type cording with neither a history of surgery nor any other potential etiology. The only plausible contributing factor appeared to be the individual's strenuous arm workouts. An ultrasound showed no evidence of a blood clot, and an MRI was negative. The cord eventually resolved within 2-3 months after a period of rest, following a physician prescribed reduction in the intensity and frequency of the arm exercise program, and doing therapeutic physical therapy that involved rolling a ball along the cord to "break it up."

A healthy 41-year old male from Belgium (Greek origin) noticed asynchronous cord-like structures along his left trunk and right axilla. There was no history of infection, axillary operation, or problems with thyroid, kidney, or liver. The individual had a normal BMI (23.7kg/m^2) and was an avid long distance runner, training for 2-3 marathons and ultra-marathons a year. He reported a recent history of olecranon bursitis in the left arm, which he attributed to a recent fall while training for a demanding ultra-marathon. About a month later, he noticed a 5 cm cord like structure on his left trunk running from the upper ribs to the abdomen. The cord-like structure diminished after 2-3 months but did not completely disappear (*Fig. 1*). He then noticed a long cord running from his right axilla to his elbow which prompted him to see a physician. Blood work revealed elevated

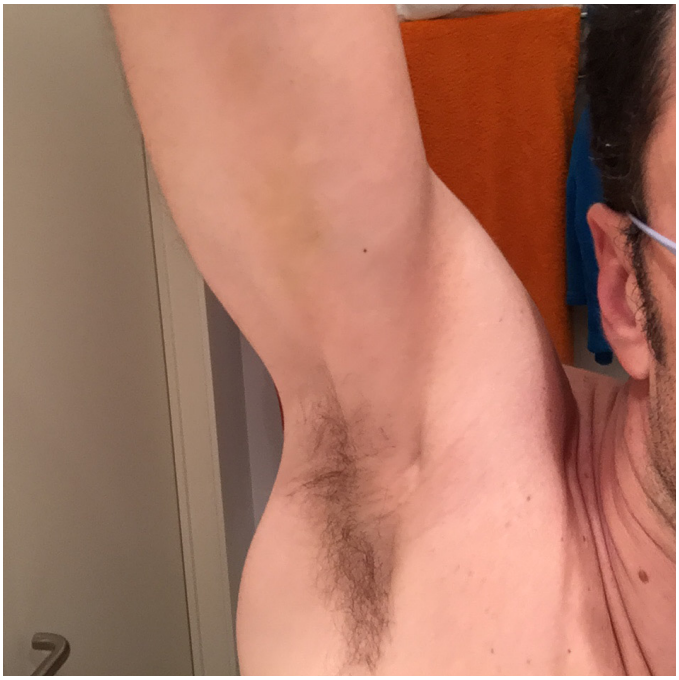

Fig. 2. Appearance of axillary cord one week post treatment with arm in abduction.

eosinophils (9.6%, 798/mm^3) and basophils (1.4%), ASAT (59 IU/L), and a positive Stallertest (i.e. allergy test). The cord was treated with manual techniques to break down the cord tissue. His range of motion improved but a cord was still palpable and visible in the axilla down the medial right arm towards the elbow a week later (*Fig. 2*).

The lymphatic system is part of or encompasses the immune system. It is a reasonable hypothesis to assume that invasion of the lymphatic system by cancer cells, viruses, or bacteria may lead to obstruction in lymphatic vessels or nodes resulting in AWS development. In these two cases above, however, it is less clear as to why strenuous activity should lead to AWS development? It has been readily accepted that moderate exercise is beneficial to the lymphatic/immune system and the general health and well-being of individuals. However, extremely strenuous, intensive exercise can adversely affect the immune system (29). Niemen et al have illustrated that the relationship between physical activity and the risk of upper respiratory tract infection results in a "U-shaped" incidence curve (30). Moderate exercise can lower the risk of infection while either minimal or excessive amounts of exercise can increase the risk of infection (30). We hypothesize that the extremely strenuous activity described in the above cases elicited an excessive immunological response. Testing of the elite male athlete revealed evidence of a hyperimmune reaction based on the positive allergen test plus elevated white blood cell counts (i.e., eosinophils and basophils). Under these conditions, the lymphatic system possibly became overloaded leading to congestion of the lymphatic vessels and cord development. The slightly elevated ASAT liver function test was considered irrelevant because physical exercise can result in transient elevations of liver function tests.

We would like to stress that moderate exercise can boost the immune system and

should be performed regularly to obtain the full beneficial effects. The development of AWS potentially associated with strenuous exercise described above is uniquely confined to a small subgroup of individuals performing elite level, high intensity exercise. Exercise should never be avoided to reduce the chance of developing AWS. In the case of an elite athlete who develops AWS, integrating appropriate rest times into their schedule and reducing the intensity of workouts should be considered to allow the body to recover. In addition, treatment by a rehabilitation therapist who specializes in lymphedema should also be considered. Further research is needed to substantiate the association between strenuous exercise and AWS development.

Cases of AWS unrelated to surgery are potentially more common than the scattered case reports would lead us to believe because cording is often undiagnosed, misdiagnosed, or ignored in many situations due to a lack of awareness or knowledge. Lack of an agreed upon name further complicates the ability to consolidate cases. The pathophysiology of cord development remains unknown but further understanding of cases of AWS unrelated to surgery may provide some insight into this perplexing condition.

CONCLUSION

Growing evidence supports the hypothesis that AWS is associated with abnormalities of the lymphatic system. We hypothesize that AWS is an excessive but otherwise normal lymphatic phenomenon related to focal areas of lymphatic obstruction. AWS is most often seen following axillary lymph node removal during cancer surgery but cases of AWS related to a non-surgical interruption of the lymphatic system also exist. Ultrasound, CT and MRI have so far been inconclusive in their attempts to unravel the pathologic anatomy and pathophysiology of AWS, but are likely to eventually give us insights that will allow us to determine the pathophysiologic basis for this troublesome and painful problem. Our perspective on this esoteric condition, which represents a considered opinion, is based on our rapidly growing clinical experience and the small amount of extant literature. Further research, hopefully multi-institutional, is needed to substantiate our theories about the physiopathology of AWS, to clarify the period of onset and duration of AWS, its association with BMI, and finally to explain the cases of AWS that are unrelated to surgery.

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