Original Article

Nature of axillary drainage fluid after axillary lymph node dissection in breast cancer

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ABSTRACT

Introduction: Prolonged postoperative axillary drainage is a common cause of morbidity after axillary lymph node dissection (ALND). There no consensus about the nature of fluid in prolonged axillary drainage. The aim of our prospective observational study was to determine the nature of axillary drainage fluid and to study the change in its composition with prolonged drainage. **Materials and Methods:** Thirty breast cancer patients scheduled to undergo ALND were evaluated by preoperative hemogram, total protein, serum albumin, serum globulin and A:G (albumin:globulin) ratio, and a complete lipid profile, which was repeated on 5th postoperative day, along with serum interleukin 1β, interleukin 6, tumor necrosis factor (TNF)-α, and interferon γ. The daily and total axillary drainage was recorded till removal of drain. The axillary fluid was evaluated for total and differential cell count, proteins, triglycerides, and cholesterol on the 3rd, 5th, and 7th postoperative day (POD), and for interleukin 1β, interleukin 6, TNF-α, and interferon γ on 5th POD. **Observations:** Axillary fluid leukocyte count increased initially but then decreased; from initial polymorpholeukocytoses, it became predominantly lymphocytes by 7th day. On the 5th POD, axillary fluid inflammatory cytokine levels exceeded serum values by several times. Cholesterol and low-density lipoprotein levels in the drain fluid increased initially and then decreased by 7th day. Total protein content, albumin level, A:G ratio, and high-density lipoprotein levels decreased significantly and continuously. Triglycerides showed progressive increment from the 3rd to the 7th day. **Conclusions:** Axillary drainage fluid is initially an inflammatory exudate which changes to nature of lymph when the drainage is prolonged. It is important to prevent lymph leakage during and after mastectomy and to minimize the intensity and duration of the first phase of wound repair to decrease the morbidity due to prolonged axillary drainage.

Key words: Axillary drainage, axillary lymph node dissection, breast cancer, seroma

INTRODUCTION

Breast cancer is a major public health problem for women throughout the world. In India, it has now become the most common cause of cancer in females in urban areas.[1]

Axillary lymph node dissection (ALND), an integral part of the management of breast cancer, is commonly associated with arm edema, paraesthesia of the medial arm and axilla, and decreased range of shoulder motion.[2,3] One of the most common cause of morbidity after ALND is prolonged postoperative axillary drainage and seroma formation.[4]

Out of the few studies done, there is no consensus about the etiology and nature of fluid in prolonged axillary drainage after ALND. Two studies have found it to be lymph on the basis of biochemical and cytological parameters,[5,6] but other studies suggest it to be an inflammatory exudate.[7-10]

It is important to know whether prolonged axillary drainage is composed of lymph-like fluid or inflammatory exudate. If the former is the case, it is important to prevent lymph leakage during and after mastectomy, whereas in the latter case care should be taken to minimize the intensity and duration of the first phase of wound repair.[11,12]

The aim of our prospective observational study was to determine the nature of axillary drainage fluid, and to study the change in composition (if any) of axillary drainage fluid with prolonged drainage, in patients with breast cancer undergoing ALND.

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MATERIALS AND METHODS

This prospective observational study was conducted at the Department of Surgery. Thirty biopsy-proven breast cancer patients with clinically palpable axillary lymph nodes, who were scheduled to undergo ALND (along with breast conserving surgery or modified radical mastectomy [MRM]), were included in the study. Excluded from the study were patients with prior axillary surgery or axillary radiotherapy, concurrent treatment with skin graft surgery, simultaneous breast reconstruction surgery, and patients on treatment with anticoagulants, antiplatelet agents, heparin, or low-molecular-weight heparin. Also excluded from the analysis were patients who developed flap necrosis or wound infection.

The study was approved by the Institutional Ethics Committee and written informed consent was taken from all patients.

All the patients in the study underwent complete physical examination, complete blood count and biochemical tests, bilateral mammography, ultrasonography of the abdomen, chest X-ray, electrocardiography, and bone scan.

After the initial work up, preoperative evaluation of the following patients' blood parameters was also done: Complete hemogram, total protein, serum albumin, serum globulin and A:G ratio, and a complete lipid profile.

In all patients, the axillary dissection was done up to level 3, along with the surgery for the primary breast tumor (MRM or breast conserving surgery).

Repeat evaluation of all patients' blood parameters was done on the 5th postoperative day, as also serum Interleukin 1β, interleukin 6, tumor necrosis factor (TNF)-α, and interferon γ.

The daily axillary drain output, the number of days of drainage, and total axillary drainage for each patient was also recorded till the axillary drain was removed. The axillary drain was removed only when the daily drainage decreased to less than 30 mL/24 h for 2 consecutive days.

Axillary drainage fluid was evaluated for cell count, total and differential cell count, proteins, triglycerides and cholesterol on the 3rd, 5th, and 7th postoperative days. It was also evaluated for interleukin 1β, interleukin 6, TNF-α, and interferon γ on the 5th day.

RESULTS

Our study was designed to study the nature of axillary drainage fluid after ALND in breast cancer.

All of the 30 patients in the study group were female. The age of the patients varied between 28 to 65 years with a mean age of 48.4 years (±10.2 standard deviation [SD]) and a median age of 48 years.

A painless lump in the breast was the presenting complaint in all the patients. The duration of symptoms varied from 2 months to 36 months with a mean of 7.32 months (±10.42 SD) and median of 4 months.

Out of 30 patients, 11 patients (36.67%) were premenopausal and 19 patients (63.33%) were postmenopausal. Two patients (6.67%) had a family history of breast cancer in a first degree relative. One patient had a family history of ovarian cancer.

On analysis of T staging of tumor, it was found that seven patients (23.33%) belonged to stage T2, three patients (10%) belonged to stage T3, and 20 patients (66.67%) belonged to stage T4. All patients were of histological subtype infiltrating ductal carcinoma.

None of the patients developed flap necrosis or wound infection.

Total axillary fluid drain output (till the drain was removed) varied between 260 and 860 mL with a mean output of 466.8 mL (±157 SD) and a median output of 410 mL. Duration of axillary fluid drainage varied between 5 and 18 days with a mean of 7.2 days (±2.99 SD) and a median of 6 days. A total of 8 out of 30 patients developed a seroma after removal of the drain, an incidence of 26.7%.

The serial change of different parameters (average of the values of the 30 patients) in axillary drainage fluid as done on the 3rd, 5th, and 7th PODs are shown in Table 1.

From the above data, it was clear that total drain output decreased consistently with time.

The total leukocyte count increased initially but then decreased suggesting that inflammation decreases with duration of drainage. On evaluating the differential leukocyte count (DLC) in the axillary fluid, it was seen that in the initial phase the axillary fluid contained predominantly polymorphs which were replaced by lymphocytes in later stage, and on the 7th POD the DLC was predominantly containing lymphocytes. It suggests that initial fluid collection was inflammatory in origin and it was replaced by lymph later on.

On 5th POD, axillary fluid contained very high amount of inflammatory cytokines (IL-1B-193.8 and TNF-α-112.6) which exceeded the serum values of these cytokines by several times [Table 2], indicating that axillary fluid

Table 1: Serial changes of the average values (+SD) of the 30 patients of the various parameters in axillary drain fluid when measured serially on the 3rd, 5th, and 7th postoperative days

	Axillary fluid			
	Day 3 (*n*=30)	Day 5 (*n*=30)	Day 7 (*n*=14)	Serial changes in the average values*
Total output (mL/day)	69 (±22)	44.5 (±21)	37.5 (±13)	↓↓
DLC (per cumm)	N79L21	N63L31	N40L50	N ↓↓ L↑↑
TLC (per cumm)	353 (±101)	372 (±137)	251 (±69)	↑↓
Avg Protein (g/dL)	3.4 (±0.3)	2.91 (±0.4)	1.7 (±0.5)	↓↓
Avg Albumin (g/dL)	2.19 (±0.3)	1.79 (±0.5)	0.8 (±0.4)	↓↓
AG ratio	1.8 (±0.5)	1.59 (±0.6)	0.89 (±0.23)	↓↓
Cholesterol (mg/dL)	49.6 (±9)	54.7 (±9)	48 (±12)	↑↓
HDL (mg/dL)	17 (±3.4)	14 (±2.1)	11 (±1.8)	↓↓
LDL (mg/dL)	27.8 (±4.2)	35.5 (±5.4)	32.4 (±3)	↑↓
Triglycerides (mg/dL)	24 (±6.2)	26 (±8.4)	29.1 (±10.1)	↑↑
IL-6 (pcg/dL)	-	252.5 (±66.3)	-	
IFN-γ (pcg/dL)	-	7.9 (±3.6)	-	
IL-1β (pcg/dL)	-	193.8 (±104.8)	-	
TNF-α (pcg/dL)	-	112.6 (±52.2)	-	

*↑ refers to an increase, while↓refers to a decrease in values. The first arrow refers to the change between the first and second postoperative readings, while the second arrow refers to the change between the second and third readings. DLC: Differential leukocyte count, TLC: Total leukocyte count, AG: Albumin globulin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, IL: Interleukin, IFN: Interferon, TNF: Tumor necrosis factor

Table 2: Comparison of cytokine levels in serum and axillary drain fluid on postoperative day 5

	Differential leukocyte count	IL-6 (pcg/mL)	IFN-G (pcg/mL)	IL-1B (pcg/mL)	TNF-A (pcg/mL)
Serum	N68L21	41.5	8.7	10.7	39.3
Axillary fluid	N63L32	252.5	7.9	193.8	112.6

IL: Interleukin, IFN-G: Interferon gamma, TNF: Tumor necrosis factor

contains very high levels of inflammatory mediators and it is an exudate in nature in the early postoperative period.

The cholesterol levels in the axillary drain fluid increased initially and then decreased on the 7th day; this also implies that inflammation was gradually decreasing.

The average total protein content in the axillary drain fluid showed a persistently decreasing trend on serial measurements.

Axillary fluid albumin level also showed a consistently decreasing trend, which suggests that axillary fluid is an inflammatory exudate in the initial stages but has the nature of lymph when drainage is prolonged.

A:G (albumin:globulin) ratio and high-density lipoprotein (HDL) levels decreased significantly and continuously in the axillary fluid. Low-density lipoprotein (LDL) levels first increased and then decreased on 7th day.

Triglycerides showed a progressive marked increment in their levels from the 3rd day to the 7th day; implying that exudate is replaced by lymph in the later stage of seroma formation, as lymph contains high level of triglycerides.

Our study suggests that axillary drainage fluid in the initial stage is an inflammatory exudate which later changes to the nature of lymph when the drainage is prolonged.

DISCUSSION

ALND has long been an integral part of the management of breast cancer. It can be done along with conservative breast surgery or as part of a MRM.[2]

ALND is commonly associated with arm edema, infection, pain, paraesthesia in the distribution of the intercostal nerve, shoulder immobility, and decreased range of arm motion. One of the most common complication and cause of morbidity after ALND is prolonged postoperative axillary drainage and seroma which might even take a few weeks to resolve completely.[2]

The incidence of seroma ranges from 10% to over 85% depending not only on how it was defined but also on the detection method employed.[13-18] Seroma formation, a common sequel to axillary dissection, has been shown to be associated with an increased incidence of wound haematoma, delayed wound healing, wound infection, lymphedema, flap necrosis, wound dehiscence, prolonged hospitalization, delayed recovery, and initiation of adjuvant therapy.[19,20]

Traditionally, lymph leakage from the upper extremity through the transected axillary lymph trunks is believed to be an important factor in fluid secretion and seroma formation, and postoperative arm use in acting as a pump that forces large quantities of lymph into the empty axillary fossa.[4]

Through a systematic review of literature, pooling of

the available data was felt to be inappropriate not only because of paucity of high-quality evidence but also due to considerable variability in the approach and methodology used to determine the etiology of seroma. There have been only few studies investigating the composition of drainage fluid or seroma aspirates after ALND.[5-10]

Bonnema *et al*.,[5] did a laboratory analysis on 16 patients evaluating parameters like electrolytes, total protein, albumin, globulin, hemoglobin, transferrin, immunoglobulin G (IgG), fibrinogen, lipids, blood cells, glucose, osmolality, creatinine, and phosphokinase in axillary drainage fluid on the 1st, 5th, and 10th POD. They came to a conclusion that seroma fluid seemed to be peripheral lymph like fluid. However, the cell content was somewhat different from that of lymph and it contained no fibrinogen.

Tadych and Donegan[6] did a laboratory analysis on two patients evaluating parameters like proteins and cell count in aspirated fluid from patients with protracted seroma; he found that the aspirates had the characteristics of lymph.

Watt-Boolsen *et al*.,[9] studied 27 patients and evaluated concentration of leucocytes, granulocytes, lymphocytes, and IgG in drainage fluid and seroma aspirates. He found that seroma is not an accumulation of serum but an exudate. This exudate is an element in an acute inflammatory reaction, that is, the first phase of wound repair, and seroma formation reflects an increased intensity and a prolongation of this phase.

McCaul *et al*.,[10] studied 18 patients and evaluated red and white blood cells, total protein, albumin, globulin, cholesterol, triglycerides, calcium, gamma-glutamyl transferase and aspartate aminotransferase in axillary drainage fluid and preoperative plasma samples. He, however, reached the conclusion that seroma fluid reflects the exudative phase of wound repair.

Wu *et al*.,[7] in 2003 did an analysis on 16 patients evaluating factors like VEGF and endostatin levels in plasma and drainage fluid before, and on the 1st and 4th day after mastectomy. Local VEGF increase and endostatin decrease lead him to a conclusion that seroma is an exudate.

Jain *et al*.,[8] in 2004 evaluated 37 patients and included parameters like protein and LDH in fluid from first aspiration of seroma and found that seroma contains high amount of proteins (>30 g/dL) and LDH (>400 u/L) suggestive of inflammatory origin.

Some recent studies have evaluated the role of cytokines to find the origin of prolonged axillary drainage after ALND.

In a study done by Chow *et al*.,[21] in 29 patients who underwent MRM, drain fluid (20 mL) was collected and the levels of interleukin (IL)-4, IL-6, TNF-α and interferon-c were determined. For patients with no wound events, only IL-6 levels were elevated during the initial phase, but in the later phase the IL-6 levels dropped with a corresponding rise in TNF-α levels. In patients with flap necrosis, there was a sequential rise of IL-4 on day 1, IL-6 on day 2, and TNF-α on day 5, but only IL-4 was found to be a statistically significant factor associated with necrosis. In patients with seroma, the levels of IL-4 and interferon c were persistently low and were both statistically significant. They concluded that IL-6 and TNF-α are important in normal postoperative wound healing. IL-6 is associated with the initial inflammatory response after surgery and TNF-α maybe more related to the later phase of wound healing. IL-4 and interferon-c may be associated with postoperative necrosis and seroma.

In another study done by Baker *et al*.,[22] 73 samples of acute wound fluid were collected from 47 patients during the first three PODs following mastectomy for cancer (n = 47 on POD-1, n = 19 on POD-2, and n = 7 POD-3). Samples were analyzed by ELISA for growth factor levels (EGF, PDGF, bFGF, TGF-beta1, VEGF), interleukin-6 (IL-6), matrix metalloproteinases (MMPs-2, -3, -9), and the tissue inhibitor of metalloproteinase 1 (TIMP-1). The levels of EGF, bFGF, PDGF, and interleukin-6 peaked on POD-1, with a significant decrease by POD-3, while total and active MMP-2, MMP-3, and tissue inhibitor of metalloproteinase 1 showed a progressive and significant increase from the 1st to the 3rd day. The wounds that later developed an infection (11%) were found to have a significantly lower PDGF and EGF on day 1 (PDGF, median 169 pg/mL [range, 86-2,595]) than noninfected wounds (2,098 [17-66,506] $P < 0.05$, Mann-Whitney U-test). Sixty-two percent patients developed a seroma and the levels of bFGF were significantly less in these patients (441 pg/mL [45-4,108]) than in those patients where there was no seroma (807 [245-3,133] $P < 0.05$). The levels of certain growth factors in acute wound fluid maybe an important markers for wound outcomes.

Recent advances have enabled study of cytokines in axillary fluid which play a role in wound repair and wound healing. The major proinflammatory cytokines that are responsible for early responses are IL 1-α, IL 1-β, IL-6, and TNF-α. On analyzing the cytokine levels of axillary fluid in our study, it was seen that axillary fluid contained very high levels of inflammatory cytokines (IL-6-252.5, IL 1B-193.8, and TNF-α-112.6) which exceeded by several times the value of these cytokines in serum. This suggests that in the initial stages, the axillary fluid is inflammatory in origin.

To the best of our knowledge, there is no consensus about the nature and etiopathogenesis of axillary drainage fluid and of any change in its composition with prolonged

drainage. There is an incomplete knowledge of factors that influence prolonged axillary drainage. It is important to know whether prolonged axillary drainage/seroma is composed of lymph like fluid or inflammatory exudates. If the former is the case, it is important to prevent lymph leakage during and after mastectomy, whereas in the latter case, care should be taken to minimize the intensity and duration of the first phase of wound repair.

Our study shows that axillary drainage fluid in the initial stages is an inflammatory exudate which later changes to the nature of lymph when the drainage is prolonged. This suggests that routine use of anti-inflammatory agents in initial 5 days after surgery could reduce the inflammatory phase and possibly reduce duration and quantity of axillary drainage after ALND. Meticulous intraoperative technique to prevent lymph leakage and routine use of postoperative compression stocking in the ipsilateral upper limb might also help reduce lymphatic leakage after ALND.

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