Non-Hodgkin lymphoma of the breast is an uncommon entity accounting for approximately 0.5% of malignant breast neoplasms and around 3% of extranodal lymphomas. Most cases of anaplastic large cell lymphoma (ALCL) of the breast have been associated with breast implants, and a few ALCL arising de novo in patients without breast implants have been reported. We report a case of a 19-year-old female who presented with a lump in the right breast of 3 months’ duration. Examination revealed an Eastern Cooperative Oncology Group performance status of 2 and a 6x5 cm² lump in the right breast. Lumpectomy revealed large neoplastic cells positive for CD30, EMA, CD5, and anaplastic lymphoma kinase (ALK), suggestive of anaplastic large cell lymphoma. The patient underwent lumpectomy followed by 6 cycles of anthracycline-based chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone 3 weekly. On follow up, this patient had an event-free survival of 23 months. We are reporting this case of ALCL (ALK positive) in a patient with no breast implant previously, and, hence, it is of clinical importance.

**CASE**

A 19-year-old female with no premorbid illness presented with a lump in the right breast of 3 months’ duration. General physical examination revealed an emaciated lady with an Eastern Cooperative Oncology Group performance status of 2; she had pallor. There was no evidence of peripheral lymphadenopathy. The examination of the right breast revealed a firm, non-tender 6x5 cm² lump in the upper and outer quadrant. The examination of the heart, lungs, and abdomen were unremarkable. On evaluation, hemogram and serum biochemistry were within normal limits. Serum lactate dehydrogenase was found elevated (567 U/L). The patient initially underwent a fine-needle aspiration cytology of the breast lump, which showed malignant lymphoid cells with cytoplasmic vacuolation (Figure 1, Panels A and B). She later underwent lumpectomy, and the histopathologic examination showed ALCL breast with characteristic hallmark cell having embryo-like nucleus (Figure 2, Panels A and B). Immunohistochemistry showed large neoplastic cells positive for CD5, CD30, EMA, and ALK, suggestive of ALCL (Figure 3, Panels A-D). The patient received 6 cycles of anthracycline-based chemotherapy with CHOP (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², and prednisolone 100 mg/d × 5 days) every 21 days. On
follow up, this patient had an event-free survival of 23 months.

**DISCUSSION**

In 1985, Harald Stein and Karl Lennert identified this rare form of Non-Hodgkin lymphoma—a large cell lymphoma with anaplastic cytology, and expression of antigen Ki-1(CD30). Based on the expression of ALK protein, it was classified into ALK positive (+) and ALK negative (−) ALCL. ALK+ ALCL, ALK−ALCL, and primary cutaneous (C-ALCL) were included in the 2008 World Health Organization classification of lymphomas.

Among all systemic ALCLs, ALK− accounts for 15% to 50% of cases. It affects older adults with male preponderance. This is in sharp contrast to the ALK+ ALCL that involves the 20- to 30-year age group. Our case was a 19-year-old female, which is consistent with the published studies review. In ALK−ALCL, nearly half cases had lymph node involvement at diagnosis. Extranodal involvement was seen in only 15% to 20% cases (skin, liver, lung, pancreas, breast, and gastrointestinal tract) unlike in ALK+ ALCL where 60% cases had extranodal involvement (bone, soft tissue, bone marrow, and spleen). Both ALK+ and ALK−ALCL can affect the breast rarely as seen in our case. Most show clonal rearrangement of TCR genes t(6;7)(p25.3;q32.3) and it can also be seen in ALK−ALCL.

Among the T-cell neoplasms, 3 types of ALCL can involve the breasts, often as a part of systemic disease: ALK+ ALCL, ALK−ALCL, and cutaneous ALCL. Most cases of ALCL of the breast have been associated with breast implants, and to the best of the published studies search, ALCL arising de novo in patients without breast implants has been reported in 27 cases previously as described in a detailed review by Lazzeri et al. in 2011. In the 27 cases described in case reports dating from 1993, 25 were females and 2 were males, 7 were in the age group of 10 to 30 years, 9 were in the age group of 30 to 50 years, 5 were in the age group of 50 to 70 years, and 2 were in the age group of 70 to 90 years. The age of 4 patients was not known. Of the 17 cases whose ALK status was known, 9 had ALK− and 8 ALK+. Among the 8 patients whose treatment details were known, 1 underwent excision of mass, the rest underwent anthracycline-based chemotherapy with or without rituximab. The details of ALCL breast with no breast implant case reports published are summarized in Table 1.

Breast implant–associated ALCL (seroma-associated ALCL) commonly arises within the fibrous capsule surrounding a breast implant and is accompanied
Table 1. Summarizing various studies of ALCL breast without breast implants.

| Study                      | Age in y/Sex | Breast (L/R/bilateral) | ALK                  | Treatment                                      | Outcome                  |
|----------------------------|--------------|-------------------------|----------------------|------------------------------------------------|--------------------------|
| Present study (2013)       | 19/F         | R                       | +                    | CHOP                                           | EFS (23 mo)              |
| Daneshbod et al (2010)     | 16 y/F       | R                       | +                    | CHOP                                           | Succumbed to disease     |
| Miranda et al (2009)       | 61/F         | L                       | _                    | R-CHOP + anti-CD 30 antibody                   | Alive with disease (2 y) |
| Kelten et al (2009)        | 33/F         | L                       | _                    | CHOEPE + DHAP + SCT                            | Alive with disease (30 mo) |
| Krishnan et al (2009)      | 33/F         | R                       | +                    | chemotherapy                                    | Alive with disease (30 mo) |
| Pereira et al (2002)       | 92/F         | L                       | _                    | Excision of lump + CHOP/MTX                   | Died of disease after 3 mo of diagnosis |
| Aguilera et al (2000)      | 13/F         | L                       | +                    | Excision of mass                               | Died of disease after 5 mo of diagnosis |

ALK: Anaplastic large cell kinase; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; CHOEPE: cyclophosphamide, doxorubicin, vincristine, prednisolone, etoposide; DHAP: dexamethasone, cyctosine arabinoside, cisplatin; EFS: event-free survival; F: female; MTX: methotrexate; L: left; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R: right; SCT: stem cell transplantation; y: year.

with an effusion. Various definitions have evolved to understand this entity and are now defined as not a disease of breast, rather disease of the fibrous capsule surrounding the implant.8 Hence this entity should be suspected by the clinician if a patient with a breast implant presents with a breast tumour and an effusion. Immunophenotypic analysis shows that neoplastic cells are of T-cell lineage and exhibit a uniform and strong expression of CD30. The ALK−ALCL with implants has a localized presentation with an indolent course. These patients respond well to implant removal and excision of the fibrous capsule around the implant. In patients with mass adjacent to implant have an aggressive course and are treated with a multi-modality approach, which involves surgery followed by anthracycline-based chemotherapy with or without radiation therapy.9

The treatment of ALK−ALCL is in the lines of T-cell lymphomas as it is uncommon, has a wide spectrum of clinical presentation, and there is no randomized trial till date. CHOP is the most commonly used regimen to treat systemic ALCL. Our patient underwent lumpectomy followed by 6 cycles of CHOP therapy and is currently has an EFS of 23 months on follow-up. ACVBP chemotherapy (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) followed by a consolidation therapy with high-dose methotrexate, ifosfamide, etoposide, asparaginase, and cytosine-arabinoside or m-BACOD (methotrexate, bleomycin, Adriamycin, cyclophosphamide, vincristine, dexamethasone) have also been tried with good results. In a German high-grade aggressive non-Hodgkin lymphoma study, 320 patients were studied with peripheral T-cell lymphoma from 7 phase II and III trials, in which a total of 113 cases of ALK−ALCL were included, who were treated with CHOP, CHOEPE (CHOP plus etoposide), or intensified CHOEPE (High-CHOEP/14/21 or Mega-CHOEP). The 3-year EFS and overall survival (OS) were 46% and 62%, respectively, in patients with ALK−ALCL.10 There are no phase III trials reporting whether transplantation upfront, or at first remission, or during relapse would be beneficial. Pralatrexate, brenuximab vedotin, combinations of bortezomib with gemcitabine, vorinostat, and single-agent lenalidomide are being tried in relapsed peripheral T-cell lymphomas and ALCL with variable response.11

To conclude, ALCL of breast is a rare disease and may masquerade as a breast cancer. Biopsy including immunohistochemistry is essential for early diagnosis. There is increased incidence of ALK−ALCL following a frequent use of breast implants. Patients with breast implants should be monitored regularly, and an early diagnosis with appropriate treatment may improve the outcome. However, even in patients without breast implants, ALCL can affect the breast and should be considered in the differential diagnosis because early treatment can improve the OS.
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