

Breast cancer in a patient with Kindler's syndrome

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Abstract

Breast Cancer (BC) has associated risk factors and genetic factors like BRCA1, and BRCA2. Many benign and malignant disease processes are found concurrently with BC and believed to be additional risk factors like gall bladder stones (cholelithiasis), hypertension, diabetes mellitus, cerebrovascular lesions, arthritis, spine and spinal cord degenerative lesions, infertility, depression, sleep disturbances, obesity, autoimmune diseases (SLE), and thyroid diseases. There are some malignant disease associations like synchronous or metachronous ovarian, colonic and endometrial tumours with Breast cancer.

Kindler Syndrome (KS) is a rare autosomal recessive genetic disorder manifesting as generalized dermatoses, described in 1954 by Theresa Kindler. KS is associated with acral skin blistering inducible by trauma, mucosal inflammation, photosensitivity, progressive pigmentation, telangiectasia, and skin atrophy (Poikiloderma). Repeated and progressive inflammation and subsequent fibrosis leads to ectropion, esophageal, anal, urethral, and vaginal stenosis and dryness.

About 100 cases of Kindler syndrome have been reported in literature so far some from Arab World as well. Pathobiology of Kindler syndrome is not well understood. There are defects in KIND1 gene on chromosome 20. This gene expresses itself in basal keratinocytes, where it encodes a protein, called Kindlin 1.

We report the second only case of Kindler's syndrome having breast cancer. These very very rare combinations have diagnostic issues, management restrictions, prognostic and follow up implications.

Keywords: Kindler's syndrome, Breast Cancer, Oman, The Royal Hospital, BC, KS.

Introduction

Breast Cancer (BC) is the commonest female malignancy

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the World over and especially in the developing World.¹ There are associated risk factors and genetic factors like BRCA1, and BRCA2.¹⁻⁴ Many benign and malignant disease processes are also found concurrently with BC and are believed to be associated with and regarded as additional risk factors. The BC is found more in patients with gall bladder stones (cholelithiasis), hypertension, diabetes mellitus, cerebrovascular lesions, arthritis, spine and spinal cord degenerative lesions, infertility, depression, sleep disturbances, obesity, autoimmune diseases (SLE), and thyroid diseases.² There are some malignant diseases associations like synchronous or metachronous ovarian, colonic and endometrial tumours. Patients having melanoma are at 1.4-2.7 times higher risk of developing BC, related to p16 gene mutations.³

Kindler Syndrome (KS) is a rare autosomal recessive genetic disorder manifesting as generalized dermatoses. It was described in 1954 by Theresa Kindler.^{5,6} KS is generally associated with skin blistering in predominantly acral distribution inducible by trauma, mucosal inflammation, and photosensitivity.^{7,8} Other features include progressive pigmentation, telangiectasia, and skin atrophy (Poikiloderma). Periodontal inflammation and premature loss of teeth is also often seen. Repeated and progressive inflammation and subsequent fibrosis leads to ectropion; esophageal, anal, urethral, and vaginal stenosis and dryness.^{5,7-10}

About 100 cases of Kindler syndrome have been reported in literature so far.¹¹ In the Arab World cases have been reported from Algeria (3 families 7 patients), Iraq (Two Kurdish Jewish families with 4 patients), Saudi Arabia (one family with 11 patients), and Tunisia (One family 2 patients).¹² Pathobiology of Kindler syndrome is not well understood. There are defects in KIND1 gene on chromosome 20.¹² This gene expresses itself in basal keratinocytes, where it encodes a protein, called Kindlin 1. Many mutations in this have been identified in KS.¹² Kindler syndrome is associated with some malignant tumours like skin, larynx, oropharynx, bladder etc.¹¹ Kindlin 1 is a regulator of TGF-beta and through this mechanism it plays a role in pulmonary metastasis of breast cancer and lung cancer.¹³ In addition, in lung cancer Kindlin 1 has an opposing role to Kindlin 2, which blocks the invasive growth of the tumour.¹⁴

We report a young female pre-menopausal patient of Kindler syndrome, who developed breast cancer. This is the 2nd case reported so far in literature. There are specific and unique issues related to diagnosis, management, screening and follow up in this scenario; which are discussed in detail.

Case Report

A 32 year old Omani female was diagnosed as W.K. Kindler syndrome since birth with generalized skin lesions. Initially she received topical and systemic corticosteroids. She was still under dermatology care with only current advice of avoidance of sunlight and no additional medicinal treatment (Figure-1). As per past surgical history, she had right clavicle fracture due to road traffic accident about 3 years back. She presented with progressive painless left breast lump in the upper outer quadrant of one month duration. She had a significant positive family history as one 1st cousin died with breast cancer, and her aunt had synchronous breast and endometrial carcinoma.

A mammogram and ultrasound breast demonstrated a 3.2cms lesion in upper outer quadrant of left breast BIRAD 4. A FNA (Fine Needle Aspiration) was reported as benign. A left breast lumpectomy was performed. Histopathology examination revealed an Invasive Ductal Carcinoma with in situ component and R1 resection (residual lesion seen microscopically). Post-operative follow up showed a 4 X



Figure-1: Skin Pigmentation and atrophy seen in the skin due to Kindler's syndrome (Chronic inflammation).

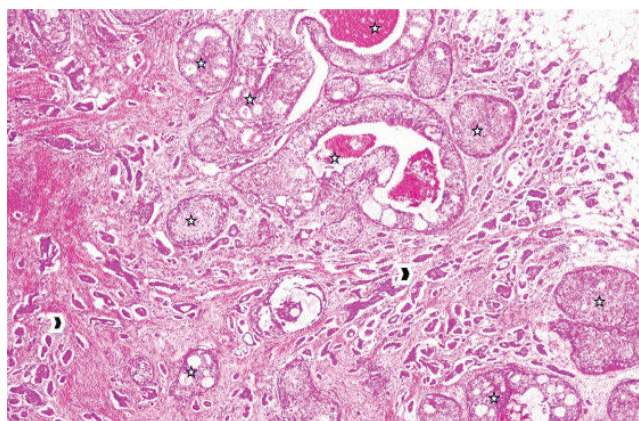


Figure-2: Infiltrating carcinoma NOS with solid, cribriform and comedo types of intermediate and high grade ductal carcinoma in situ. HE 20X.

4cms seroma, which was drained.

She was counseled about further management, and advised mastectomy in view of the co-morbid condition along with positive family history. She strongly refused mastectomy, and thus underwent quadrectomy and SLN (sentinel lymph node biopsy) on 14/10/2011, at a private surgical facility. Histopathology examination showed foci of high grade DCIS (ductal carcinoma in situ), suture granuloma, a deep resection margin at 1 mm. SLN biopsy showed reactive changes. There was a 2 x 1.7cms fibro adenoma in the left axilla.

At this point she was referred to Medical Oncology for further management. She was first seen in Oncology multi-disciplinary clinic, National Oncology center - the Royal hospital Muscat Sultanate of Oman in the 3rd week October, 2012 (18/10/2012). A new mammogram showed post-surgical changes only. There were clinically significant telangiectasia, blisters and sloughing of skin of variable intensity all over her body. She was found to be very anxious and unstable, having some psychological issues. Bone scintigraphy showed a suspicious isotope uptake in D7 (Dorsal 7th) vertebra and right 4th costovertebral junction. The bone scan images were reviewed in multidisciplinary tumour board with Nuclear Medicine consultant and Radiologist. These lesions were asymptomatic and it was concluded that these uptake are not due to metastasis but correlated to traffic accident injury that patient had 3 years back. Staging CT Scans of neck, chest, abdomen and pelvis were done and found to be negative for any metastatic lesion. The plan of management was discussed at multi-disciplinary clinic and tumour board. Due to unique clinical scenario, positive surgical margin, and a limitation of giving adjuvant radiation therapy to breast

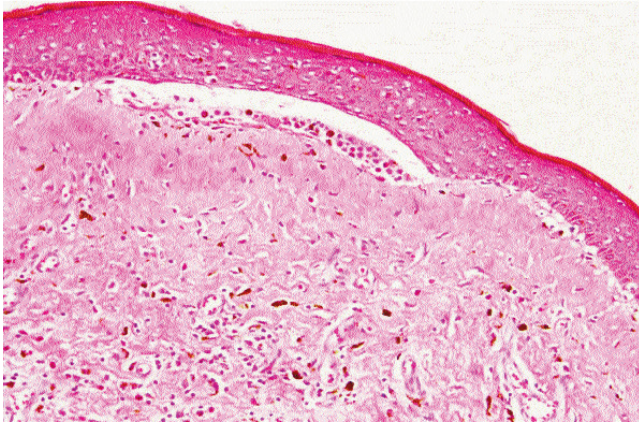


Figure-3: Skin with mild hyperkeratosis, and atrophy. There is sub-epidermal bulla with cavity containing eosinophils and neutrophils. The dermis shows telangiectasia, dermal melanophages, lymphocytic and eosinophilic infiltrate. HE x20 objective.

she was advised mastectomy.

She finally agreed for mastectomy, which was done in December 2012. Final pathologic diagnosis with staging was IDC with high grade DCIS pT2 (3.2cms) N1 (1/7 nodes showing metastatic deposits) M0, ER+ PR+ Her2 ++ on IHC and FISH Negative. (Figure-2 and 3)

The patient after mastectomy did not require adjuvant radiotherapy as per pathologic stage. We did not advise any systemic chemotherapy with cytotoxic drugs due to expected high risk of profound toxicity, as the metabolizing potential for cytotoxic drugs in this patient is unknown. It was also realized that the only reported case in literature had life threatening toxicity with systemic chemotherapy. She was started with and is currently on hormonal therapy, taking 20 mg tamoxifen (anti estrogen) orally daily. She is in regular 3 monthly follow up at our clinic and last seen in our breast oncology clinic on 29th November 2016. Her breast cancer is under control with no evidence of disease clinically, serologically and radiologically. Her only complaint is dryness of mouth and dysphagia to solids.

Discussion

Kindler syndrome (KS) is a rare autosomal recessive genetic disorder presenting as progressive dermatoses, skin blisters, poikiloderma, pigmentation, and photosensitivity.^{5-7,9,10} There can be periodontal inflammation and premature loss of teeth. Repeated progressive inflammation and fibrosis can cause esophageal, anal, urethral, and vaginal stenosis. KS is a subject of extensive genetic studies and many genetic defects are described in these patients. FERMT-1 gene mutation leads to deficiency or defects in FFH-1. FERMT is

linked to cell migration, proliferation and adhesion.^{5,7} Mutations in FERMT-1 genes described in KS are believed to predispose for other malignancies like squamous cell carcinoma of sun exposed skin, and transitional cell cancer of urinary bladder. About 10% of KS patients are at increased risk of other tumours like breast, colon, and lung.^{4,15-17}

Breast cancer in KS is very rare, and our reported case is only the second one so far described in literature.^{4,6} The only other case reported is a synchronous bilateral breast cancer from Turkey.⁶ There are definite and challenging management issues, yet there are no defined guidelines of management due to rarity of disease combination.

The patients with KS have photosensitivity.⁹ The skin and mucosal lesions can be induced, reactivated or get worsened by radiation. There is obvious limitation to the use of radiology as diagnostic or follow up evaluation tool (X-rays or CT Scans). The breast conservative surgery is not a preferred option because essential post-operative radiotherapy can't be delivered. These KS patients are also reported to be poor in metabolizing cytotoxic drugs, however the data for each and every individual drug is not yet available.^{6,9,15-17} Chemotherapy is therefore more toxic than a normal individual related to inherent defects in enzymes and drug degradation pathways. There are obvious issues of dose adjustments, total avoidance, and exaggerated unmanageable often fatal drug toxicity. There is also a chance of reactivation of disease with cytotoxic therapy. The hormonal therapy by anti-estrogens (Tamoxifen) is believed to be much safer so far.

The only reported case when given chemotherapy based on epirubicin, trastuzumab, and cyclophosphamide; tolerated it well up to 3 cycles. The patient however had life threatening diarrhoea with docetaxel and treatment had to be stopped. The patient was given only hormonal therapy thereafter and maintained on it.⁶

Should a KS patient be subjected to an early screening for breast CA (mammography/MRI), colonic CA (endoscopy), endometrial CA, and lung CA? This is a question that poses itself with no clear answer at present. It is however advisable for these patients to be screened regularly, starting much earlier than the normal population.⁶

The patient reported in this article, was diagnosed at an early age with KS. She was followed up closely by dermatology still having some skin lesions and pigmentation. She was heavily treated with corticosteroids. She was married but divorced. The Kindler Syndrome's skin manifestations, prolonged steroids use, associated social issues, and subsequent breast cancer

contributed to her anxiety and emotional status. There were challenging decision issues due to denial and reluctance as demonstrated with initial conservative surgery, followed by completion of surgery.

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Conflict of Interest: None.

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