

Rare malignancies in Eastern India, socio-economic impact

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Abstract

The etiology of cancer is multifactorial. Various factors, including physical carcinogens, chemicals and viral carcinogens affect patients with known predisposing factors who subsequently develop malignancies. Here is a retrospective study of 18 patients who developed rare malignancies in clinical situations like xeroderma pigmentosum, tuberous sclerosis, neurofibromatosis, hereditary multiple exostosis, second malignancies due to radiotherapy and chronic irritation. The predisposing factors like chronic infection in leprosy, filariasis, poverty and ignorance leading to the chronicity of the lesion, lack of available health care facilities and socio-cultural background, *i.e.* consanguinity marriage in some community are responsible for the development of these rare malignancies. They were treated at A.H Regional Cancer Centre, Cuttack, Odisha, which is located at Eastern part of India for various malignancies, between January 1989 and January 2008. Malignancies that developed in patients with the above predisposing factors are being reported here due to their rarity and to highlight the impact of socio-cultural background in developing these malignancies. Patients with above clinical situations should be kept under close observation for early detection of malignancy so their chances of survival can be improved. In addition, those oncogenic stimuli that initiated or propagated the malignancies, due to socio-economic factors, should be addressed promptly to prevent their eventual development.

Introduction

The etiology of cancer is multifactorial. Various factors like physical carcinogens, chemical carcinogens, viral carcinogens and oncogenes play important roles in carcinogenesis. Patients with different genetic disorders like xeroderma pigmentosum (XP), tuberous sclerosis (TS), neurofibromatosis type I and II (NF I and II) and hereditary multiple exostosis

(HME) are more prone to develop malignancies which are otherwise rare in incidence.

With the advent of multidisciplinary approaches and newer developments in the treatment of cancer, the survival rate of such patients has improved. However, the incidence of secondary malignancies due to treatment is becoming increasingly recognized. Secondary malignant neoplasms arise due to chemotherapy, radiotherapy, or both. These are distinct entities having a definite picture of malignancy; they are histologically different from, and lack metastatic deposits from, the primary neoplasm.^{1,2} The incidence of treatment related malignancies, though rare, is being reported with greater frequency of late.

Here, we present a retrospective study on 18 patients having uncommon malignancies that developed in XP, TS, NF I and II, HME, cancer related treatment, and chronic infection who subsequently developed malignancies. Exposure to sunlight, consanguineous marriage, infection with leprosy, filariasis, lack of knowledge of development of such malignancies on above genetic disorders, poor access to health care facilities in remote village areas and poverty are the various factors to develop these malignancies in rare situations. These cases merit reporting and documentation for their rarity.

Materials and Methods

Eighteen patients who developed malignancies in different clinical conditions like XP, TS, NF I and II, HME, prior radiotherapy, chronic infection and who were treated during the period Jan 1989 to Jan 2008 were analyzed retrospectively. Table 1 summarize the clinical data of the patients with respect to age, sex, genetic disorder and underlying predisposing factor, site of development of malignancy, interval between development of underlying disease and the development of malignancy, and the histopathology of the malignancy.

Results

Out of 18 patients who subsequently developed different types of malignancies, 4 had XP, 3 had tuberous sclerosis, 6 had NF, 1 had multiple exostosis of bone, 1 had astrocytoma grade II of the right frontoparietal lobe (treated with surgery followed by radiation), 1 had carcinoma of cervix of stage IB (treated with weekly cisplatin and radiation), 1 had ectopia vesicae, 1 had filariasis of the scrotum and 1 had leprosy (Table 1).

Patients with XP in this study subsequently developed carcinoma of the skin, conjunctiva

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and left lateral border of the tongue (Figure 1A-D). All patients developed squamous cell carcinoma except for one, who developed basal cell carcinoma, squamous cell carcinoma, and melanoma of the skin. The mean interval between the appearance of XP and the detection of malignancies was 10 years.

Out of the 3 patients with tuberous sclerosis, 2 patients developed sub ependymal giant cell astrocytoma adjacent to the foramen of monro and right lateral ventricle while 1 developed clear cell carcinoma of the left kidney (Figure 2A-F). The mean interval of the development of the malignancies was 23 years.

Six patients with neurofibromatosis were assessed in this series, of which five had type I disease and one had type II NF. Two patients with type I NF developed neurofibrosarcoma, another two developed carcinoma of the breast (Figure 3A,B) and the remaining patient developed carcinoma of the thyroid (Figure 3C). The patient with type II NF had bilateral acoustic tumor, spinal cord astrocytoma, and osteosarcoma of right arm (Figure 3D-F).

A 46 years old male who had developed chondrosarcoma of the left femur was found to have multiple exostosis of the different long bones (Figure 4A,B). This was consistent with his family history.

One patient with astrocytoma grade II of the right fronto-parietal area developed transitional meningioma at the right frontotemporopari-

etal area (site of the radiation portal) 14 years after the surgery and external beam radiation. One patient with ectopia vesicae developed adenocarcinoma at the ectopia vesicae 42 years after birth (Figure 5A). Also, presented here is a very unusual case of a patient with elephantiasis of the scrotum, who subsequently developed squamous cell

carcinoma of the scrotum 38 years after the development of elephantiasis (Figure 5B). The reported series also includes a 52 years old male with leprosy. He had a persistent trophic ulcer over the plantar aspect of the left foot and subsequently 12 years later he developed squamous cell carcinoma over that trophic ulcer (Figure 5C).

Discussion

All 18 patients have been reported from Cuttack, Odisha which is located in eastern part of India. The total number of population in Odisha is 44 millions having sex ratio 978 females/ 1000 males. The *per capita* income of



Figure 1. Xeroderma pigmentosum (XP) with malignancies. A) XP with squamous cell carcinoma of face. B) XP with squamous cell carcinoma, basal cell carcinoma and melanoma of face and squamous cell carcinoma of conjunctiva. C) XP with squamous cell carcinoma of conjunctiva. D) XP with squamous cell carcinoma of anterior tongue.

the people of Odisha is Rs 28,384 in contrast to the national average of Rs 39,904. Literacy rate is 73.5%. Regarding health care facilities, there are 3 Govt. Medical Colleges, one Regional Cancer Centre, one pediatric institute, 32 district head quarter hospital, 22 sub-divisional hospitals, 231 community health centers and 117 primary health centers.

XP is an autosomal recessive disorder. Patients with XP presented with cutaneous, ocular, and neurological manifestations at the age of 1-2 years and cutaneous malignancies at the age of 8 years.³ Ultraviolet radiation of wavelength 290-320 nm produces dimerization between adjacent pyrimidine analogues producing photoproduct cyclobutane-pyrimidine dimers and pyrimidine-pyrimidine photoproducts. Patients with XP have a reduced or defective excision repair of pyrimidine dimers, leading to higher incidence of cutaneous malignancies in areas exposed to sun. Cleaver and colleagues revealed that besides cutaneous malignancies, patients with XP develop carcinoma of the tongue, medulloblastoma, and breast carcinoma.⁴ In a retrospective analysis of 120 patients of XP, Moussaid and colleagues observed that 153 skin tumors were diagnosed in 96 patients, out of which basal cell carcinoma was found in 32.6%, squamous cell carcinoma in 33.9%, and melanoma in 11% of the patients.⁵ All 4 patients in this report developed XP at the age of 2 to 4 years. The mean interval of development of malignancy was 10 years in this study. Three patients developed oculocutaneous malignancies and one patient had carcinoma of the tongue. All the patients had developed squamous cell carcinoma except one patient who had squamous cell carcinoma, basal cell carcinoma, and melanoma of the skin. Case no. 2 and 3 were brother and sister. Their parents had consanguineous marriage as reported. The incidence of consanguineous marriage is about 32 to 34% in south India, which is close to the south parts of Odisha from where the patients belong. As reported the incidence of XP is high due to consanguineous marriage of the parents. Besides due to lack of knowledge and awareness program, these patients were always exposed to sunlight and developed various oculo cutaneous malignancies.

TS is a hereditary autosomal dominant neurocutaneous disorder characterized by the clinical triad of seizure, mental retardation, and facial adenoma sebaceum. Additional lesions are shagreen patches, periungual or subungual fibromas, and *café-au-lait* spots. 10-15% patients with TS also have giant cell astrocytomas.⁶ These are mostly due to transformation of tubers (located at and around the foramen of monro) to solid, benign tumors. Visceral malignancies like clear cell carcinoma

of the kidney, sarcomatoid and malignant angiomyolipoma of the kidney are also observed in tuberous sclerosis. In this series, 2 patients had subependymal giant cell astrocytomas as shown by histopathology and one patient had clear cell carcinoma of the kidney. The mean interval of the development of these malignancies was 23 years. The impact of socio economic factors to develop the malignancies in TS could not be established in these

cases. NF are inherited genetic disorders that predisposes the affected individuals to benign and malignant neoplasms. They may involve any system and any tissue, ectoderm, mesoderm, or endoderm. The genes for NF-1 & NF-2 are located on chromosomal 17q and the center of the long arm of chromosome 22 respectively. NF1 is associated with tumors of Schwann cells, glial cells, and adrenal medulla, while NF2 is associated with Schwann cells of

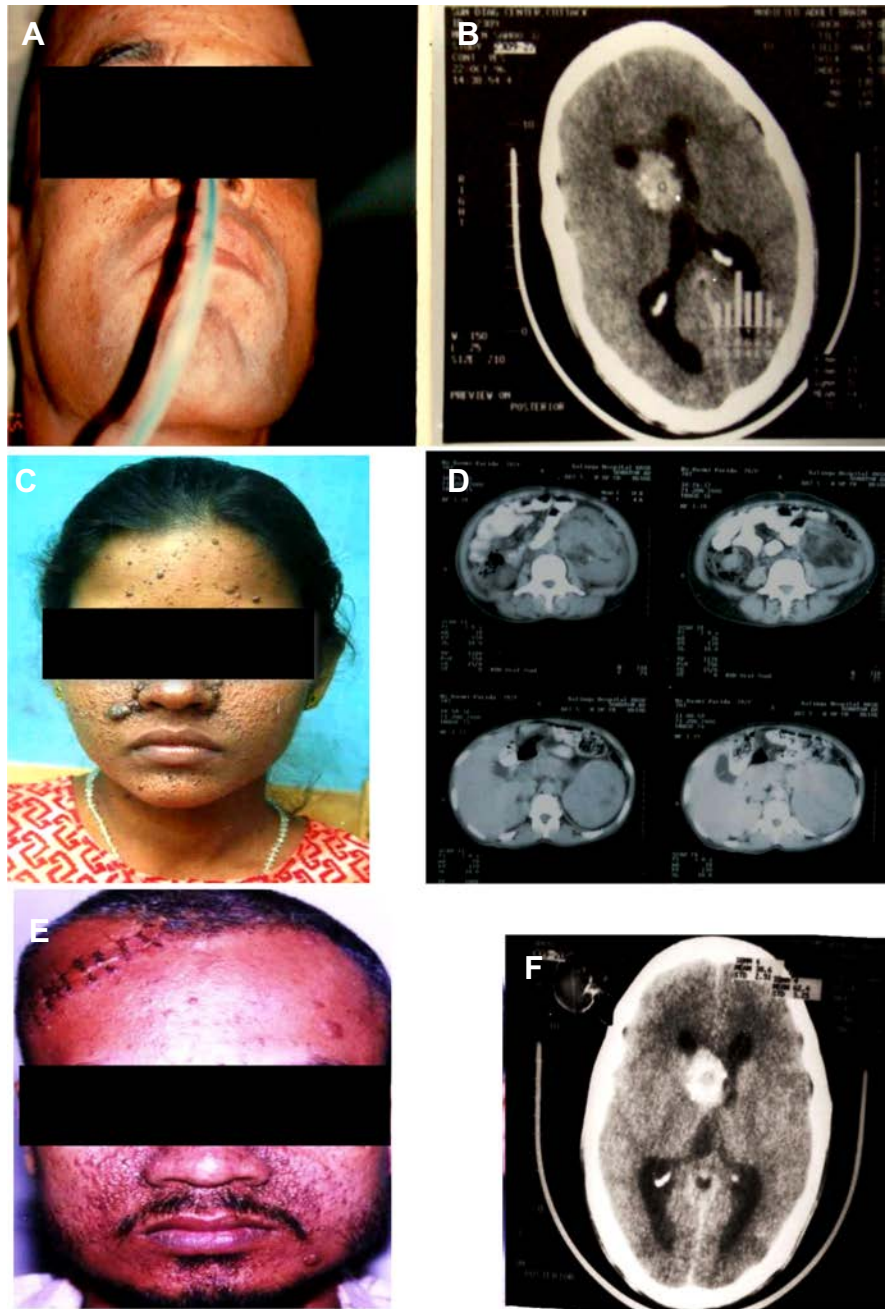


Figure 2. Tuberos Sclerosis (TS) with malignancies. A-B) TS with subependymal giant cell astrocytoma. C-D) TS with renal cell carcinoma of left kidney. E-F) TS with subependymal giant cell astrocytoma.

VIII cranial nerve and meninges. NF1 has a prevalence of 1:3500 persons worldwide. Patients with NF1 are predisposed to develop low-grade gliomas, including optic nerve gliomas, neurofibromas, and nonacoustic schwannomas. NF2 has an incidence of 1:40,000-50,000 and patients are predisposed to develop acoustic neuromas, meningiomas and neurofibromas.

The association of breast carcinoma and papillary carcinoma of thyroid with NF1 is very uncommon. Invernizzi and colleagues published a case report on association of GIST, breast carcinoma, and schwannoma. They opined that although there is high incidence of neoplasms in the central and peripheral nervous system associated with NF1, an association between NF1 and epithelial carcinomas has not been described in the literature.⁷ Few literatures have reported the association of NF1 with breast carcinoma.⁷⁻⁹ Shariff and colleagues interpreted that women with NF1 who are younger than 50 years old have a fivefold increased risk of breast cancer.⁹ The association of thyroid carcinoma with NF1 is also uncommon.¹⁰ In this series most of the patients presented to us in advanced stage of the disease due to poverty, ignorance and poor availability of health care at rural places.

HME is a heterogeneous autosomal dominant inherited skeletal disorder characterized by bony protuberances located mainly on long bones. A serious complication of HME is the malignant transformation of an exostosis to chondrosarcoma and rarely to other malignancies.¹¹ The life time risk of development of chondrosarcoma on HME is 2 to 4%.¹² Malignant transformation of exostosis to chondrosarcoma was associated with mutation of the *EXT1* gene, located on chromosome 8q24.¹³ Various authors have reported the development of chondrosarcoma over the hereditary multiple exostosis.^{14,15} Secondary chondrosarcoma occurs due to transformation of existing enchondromas mostly at the age of 20 to 40 years.¹⁵ Here, we present a case of chondrosarcoma secondary to HME. Patients with HME should be carefully followed for inappropriate growth of an inherited exostosis. Patients and their affected family members should be informed about the significant risk of chondrosarcoma at the time of genetic counseling and orthopaedic assessment and advised to have regular follow up. As the patient was illiterate and not aware of the disease, he presented to us in advanced stage of disease.

Radiation to the cranium acts as an oncogenic stimulus for the development of second malignancy. Most of the tumors develop in the radiation portals and the convexity of the brain (*i.e.* the site of maximal absorbed dose of radiation) and it is the most common site of development of radiogenic meningioma. Al-Mefty and colleagues observed that the radiation-

induced neoplasm consists of meningioma, malignant glioma, and sarcoma, but meningioma accounts for the majority having a latency period of 26.5 years. Cytogenetically, it is found to have aberrations of chromosome 1p, 6q and 22.¹⁶ The latency period of development of secondary meningioma in brain

ranges from 9.5 to 31.5 years.¹⁷ Martinez-Lage and colleagues analyzed 16 patients with radiation induced meningioma and observed that meningioma was predominant at the cerebral convexity in 9 patients, followed by the falx or parasagittal region in 4 patients and one each at the orbit and posterior cranial fossa.¹⁸ The



Figure 3. Neurofibromatosis (NF) with malignancies. A) NF 1 with carcinoma breast. B) NF1 with carcinoma breast, post radiation. C) NF1 with carcinoma thyroid. D-F) NF2 showing bilateral acoustic tumor, spinal cord astrocytoma and osteosarcoma of right arm respectively.

present authors also had reported a case of atypical meningioma that developed 13 years after the treatment in a patient with acute lymphoblastic leukemia who was treated with chemotherapy and prophylactic cranial irradiation.¹⁹ In this series the patient with astrocytoma grade II of the right fronto-parietal area developed transitional meningioma at the right frontotemporoparietal area 14 years after radiation. The patient was radiated with Co-60. Linear accelerator with 3D-CRT, intensity modulated radiation therapy (IMRT) technology was not available at the time of treatment in hospital. With the availability of modern technology like 3D-CRT, IMRT the normal tissue would have been spared and possibly such second malignancy would have been avoided. However the impact of low dose radiation in 3D-CRT and IMRT for development of second malignancy is under evaluation.

Malignant transformation due to chronicity of a lesion and altered body immunity is also evident in the literature. Ectopia vesicae is a rare congenital anomaly with an incidence of about 1 per 50,000 newborns. The 95% of patients with ectopia vesicae develop adenocarcinoma and 3 to 5% develop squamous cell carcinoma.²⁰ Chronic irritation and infection leading to metaplastic transformation of urothelium result in malignant changes in ectopia vesicae. Malignant degeneration of embryonic rests of gastrointestinal tissues can give rise to adenocarcinoma. It is also suggested that adenocarcinoma in ectopia vesicae originate from colonic epithelium covering the mucosa of the organ.²¹ The majority of the malignant tumors occur in the 4th to 5th decade.²² The present case was a 42 year old male who presented with an adenocarcinoma over the ectopia vesicae. Chronic irritation and infection leading to mataplastic changes of urothelium of urinary bladder resulting in malignancy is the most possible cause. Besides patient belongs to low income group and inaccessible health care facilities like reconstructive surgery is the additional factor for the development of adenocarcinoma over the ectopia vesicae in this case.

Lymphatic filariasis is endemic in tropical zone due to *W.bancrofti*. India contributes about 40% of total global burden of filariasis and accounts for about 50% of people at the risk of infection by *W.bancrofti*. States like Andhra Pradesh, Bihar, Gujarat, Kerala, Maharastra, Odisha, Tamil Nadu, Utter Pradesh, West Bengal contribute to 95% of the total burden of filarial infection in India. Elephantiasis of the scrotum is one of the manifestations of filariasis and is endemic in the eastern part of India. Due to tropical location and poor environmental condition these people of Eastern India are more prone for the development of the filarial infection leading to lymphedema. Lymphatic obstruction and later

on fibrosis in the lymph-logged tissue will cause this condition. In the present case due to chronic irritation over the lymphedema and also infection patient subsequently developed squamous cell carcinoma over it. Malignant changes over such nodules are not reported in

the literature. This is an uncommon case of an elephantiac nodule in the scrotum turning into malignancy after a period of 38 years.

Various authors have reported the development of squamous cell carcinoma over the trophic ulcer.^{23,24} In Odisha the farmers who



Figure 4. Hereditary multiple exostosis with malignancy. A) Multiple exostosis of right femur. B) Chondrosarcoma of lower end of left femur of same patient.

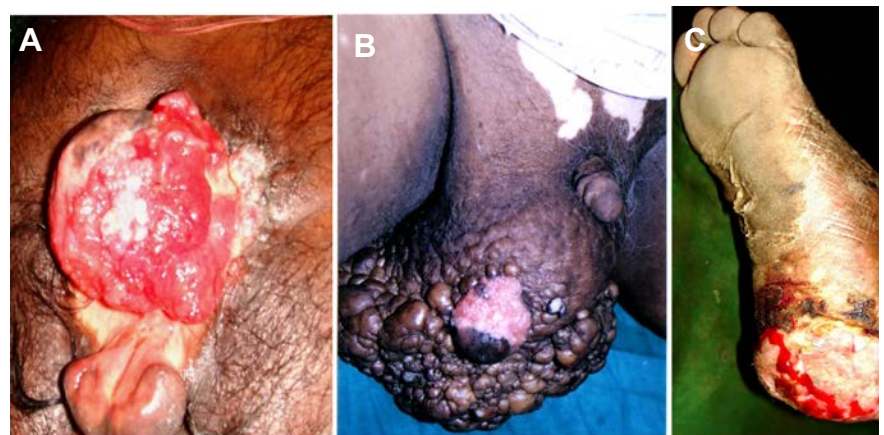


Figure 5. Chronicity of the lesion with malignancy. A) Ectopia vesicae with adenocarcinoma. B) Elephantiasis of scrotum with squamous cell carcinoma. C) Trophic ulcer of left foot with squamous cell carcinoma.

Table 1. Clinical profile of the patients having rare malignancies.

Patient	Age	Sex	Clinical diagnosis	Site of malignancy	Interval	Histopathology
1	15	F	Xeroderma pigmentosa	Skin	9 yrs.	Squamous cell carcinoma
2	18	M	Xeroderma pigmentosa	Conjunctiva, skin	14 yrs.	Melanoma, Basal cell carcinoma, Squamous cell carcinoma
3	15	F	Xeroderma pigmentosa	Conjunctiva	9 yrs.	Squamous cell carcinoma
4	14	M	Xeroderma pigmentosa	Anterior tongue	8 yrs.	Squamous cell carcinoma
5	29	M	Tuberous sclerosis	Brain	27 yrs.	Subependymal giant cell astrocytoma
6	22	F	Tuberous sclerosis	Kidney	20 yrs.	Renal cell carcinoma
7	28	M	Tuberous sclerosis	Brain	24 yrs.	Subependymal giant cell astrocytoma
8	48	F	Neurofibromatosis	Breast	48 yrs.	Infiltrating duct carcinoma
9	37	F	Neurofibromatosis	Breast	37 yrs.	Infiltrating duct carcinoma
10	44	M	Neurofibromatosis	Thyroid	At 44 yrs.	Papillary carcinoma of thyroid
11	17	F	Neurofibromatosis	Post. mediastinum	At 17 yrs.	Neurofibrosarcoma
12	21	M	Neurofibromatosis	Post. fossa, spinal Sp.cord, Right arm	At 21 yrs.	B/L acoustic tumours, astrocytoma of spinal cord, and osteosarcoma
13	42	M	Neurofibromatosis	Skull	At 42 yr s.	Neurofibrosarcoma
14	46	M	Hereditary multiple exostosis	Femur	?	Chondrosarcoma
15	55	M	Right frontoparietal astrocytoma of brain (post surgery, Post RT)	Right fronto-temporo-parietal area	14 yrs.	Transitional meningioma
16	42	M	Ectopia vesicae	Urinary bladder	32 yrs.	Adenocarcinoma
17	62	M	Filariasis of the scrotum	Scrotum	38 yrs.	Squamous cell carcinoma
18	52	M	Trophic ulcer left foot	Plantar aspect left foot	22 yrs.	Squamous cell carcinoma

belongs to low socio-economical classes are also some times infected with leprosy. Due to chronic irritation and loss of sensation over the ulcer, repeated trauma, altered cellular immunity and possibly carcinogenic potential of the dapsone (in animals) caused by the infection with *M. leprae* the patient of leprosy develops squamous cell carcinoma over this trophic ulcer. Here, we report a case of squamous cell carcinoma over the chronic, persistent trophic ulcer of the left foot, which developed 22 years after the onset of trophic ulcer. Besides the above factors, non-availability of reconstructive surgery at rural place to take care of trophic ulcer is one of the contributing factors for the development of squamous cell carcinoma.

Conclusions

Patients having XP, TS, NF, or HME are genetically more prone to develop malignancies. Long-term survivors of chemotherapy, radiotherapy or chemoradiation also develop hematological or solid malignancies. Chronicity of an ulcer and sequelae of chronic infection may lead to malignancy. These cases have rarely been reported in the literature. Patients having any of the above clinical situations should be aware of the future complications of the disease. The oncogenic agents that initiate or propagate for the development of malignancies should be avoided to prevent malignancies in the above situations.

Care should be taken to eliminate the predisposing factors that are responsible to develop the malignancy. They should be kept under close observation for early detection of malignancies to achieve better cure.

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