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Dr. Minaxi Patel
Second Year Resident,
Department of Pathology, Shri M.P. Shah Medical College, Jamnagar, Gujarat, India

Dr. Neeru D Dave
Associate Professor,
Department of Pathology, Shri M.P. Shah Medical College, Jamnagar, Gujarat, India

Dr. Pruthvi Damor
Private Practitioner,
Department of Pathology, Shri M.P. Shah Medical College, Jamnagar, Gujarat, India

Corresponding Author:
Dr. Minaxi Patel
Second Year Resident,
Department of Pathology, Shri M.P. Shah Medical College, Jamnagar, Gujarat, India

Post therapeutic changes in various malignancies

Dr. Minaxi Patel, Dr. Neeru D Dave, Dr. Pruthvi Damor

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Abstract
Background: Neo adjuvant Radiotherapy and chemotherapy can cause significant changes in the gross and microscopic appearance of malignant tissues and normal surrounding tissues. Since radiotherapy is now offered to a large number of cancer patients, pathologists are more frequently presented with such changes. Both epithelial and stromal changes can be present. Epithelial changes in the form of atrophy, apoptosis, necrosis, dysplasia and neoplasia, while stromal changes the form of fibrosis, exudates, necrosis, pattern of invasion and vessel wall thickness. These changes may interfere with recognition of microscopic residual tumor if present. With increasing use of radiation therapy in cancer treatment and longer survival of patients, assessment of radiation-associated changes in tissues and tumours has become an important issue in modern pathology.
Materials and Methods: The present study was carried out on 50 patients. Type of samples includes cytological smears and histopathological specimens received in respective cytopathology and histopathology section of the pathology department after any chemotherapy or radiotherapy.
Objective
1. To study cyto-morphological changes after chemotherapy and/or radiotherapy.
2. To differentiate secondary malignancy from radiation damage.
Results: The present study was carried out on 50 patients including 13 patients with lymph node metastasis,12 cases with head & neck region, 2 scrap smear, 9 anterior chest wall swelling, 3 cases of liver, 5 cases of lung,1 plural fluid and 5 cases of breast. The effects have been divided mainly into two, as pathological changes in tumor cells and changes in the stroma.
Conclusion: It is concluded from the findings of present study that various nuclear abnormalities reveal a statistically significantly increases with increasing chemoradiation doses and time interval. Post neoadjuvant chemotherapy, specimens revealed nuclear enlargement, nuclear shrinkage, necrosis, vacuolation of nucleus, vacuolation of cytoplasm, dyscohesion, and shrinkage of tumor cells with nuclear changes of nonviability like karyorrhexis, karyolysis, and pyknosis. Stromal reactions manifested as fibrosis, elastosis, collagenization, hyalinization, microcalcification, and neovascularization. Areas of necrosis included both vascular and avascular pattern. The stroma also revealed fibrinoid necrosis and mucinous change. Hyalinization of the blood vessel wall was a common finding.

Keywords: Post therapeutic changes, epithelial changes, stromal changes

Introduction
Radiation therapy and chemotherapy has important applications in curative, adjuvant, and palliative therapy for a wide range of malignant conditions [1]. The radical treatment of cancer by means of ionizing radiations aims at, and often appears to achieve, the sterilization of all the neoplastic cells.
High rate of cancer diagnosis through multiple modalities can overcome common barriers to timely diagnosis. Health-care providers at all levels of care should be equipped with the skills to identify cancer symptoms and perform or refer for diagnostic tests. Pathology is particularly important in cancer diagnosis; cancer treatment should not be started unless there is pathologic confirmation of cancer.
The pre-eminent efficacy of radiotherapy and chemotherapy does not, however, rely on highly selective sensitivity of malignant cells, and radiation interferes similarly with cells production in tumors and in proliferating normal tissues, which are necessarily included in the irradiated volume.
Radiation will halt the division in the proliferative sub population, but this will only be reflected in tissue malfunction when the differentiated cells have been lost by normal wear and tear. It may be manifested within days or may be latent for many months [2].

Neo adjuvant Radiotherapy and chemotherapy can cause significant changes in the gross and microscopic appearance of malignant tissues and normal surrounding tissues. Since radiotherapy is now offered to a large number of cancer patients, pathologists are more frequently presented with such changes.

Rapidly dividing cells are generally more sensitive than slowly dividing cells. Both epithelial and stromal changes can be present. Epithelial changes in the form of atrophy, apoptosis, necrosis, dysplasia and neoplasia, while stromal changes in the form of fibrosis, exudates, necrosis, pattern of invasion and vessel wall thickness. These changes may interfere with recognition of microscopic residual tumor if present [3].

With increasing use of radiation therapy in cancer treatment and longer survival of patient assessment of radiation-associated changes in tissues and tumours has become an important issue in modern pathology. Radiation induces injuries mainly through DNA damages which may affect apoptotic pathways, acute and chronic ischemia and subsequent tissue repair and fibrosis. Irradiated native cells are characterized by both nuclear and cytoplasmic enlargement, associated with degenerative changes [3].

Distinction from true neoplasia relies on low proliferative activity, relatively low nuclear–cytoplasmic ratio, and fine but vacuolated nuclear chromatin. Some pseudo-malignant radiation-associated changes in various organs, such as radio-necrosis in brain, colitis cystica profunda in colon, atypical basal cell hyperplasia in prostate, atypical vascular lesions in skin and pseudo-carcinomatous proliferations in urinary bladder, should also be recognized to avoid a misdiagnosis of malignancy [3].

Malignancies can arise within the field of radiotherapy due to genetic instability and accumulation of mutations years after completion of treatment. These neoplasms are osteosarcoma, angiosarcoma and leukaemia/lymphoma. They often present late and are associated with aggressive clinical behaviour and poor treatment response [4].

Earlier and accurate pathological diagnosis, with awareness of potential diagnostic pitfalls, is thus prudent in guiding subsequent management of malignancies. Neo-adjuvant therapy has been used in many clinical trials because it is easy to evaluate the treatment response to therapeutic agents in a short time period.

We therefore studied the radiotherapeutic & chemotherapeutic changes in various organs to support & validate the results of various authors as well as discuss new findings in our study, so that optimal use of these therapies can be instituted to overcome some of the toxicity of these therapies.

Aim and objectives

1. To study cyto-morphological changes after chemotherapy.
2. To differentiate secondary malignancy from radiation damage.
3. For recognition of microscopic residual tumor.
4. To identify radiation induced complications.

Type of study: Prospective & Retrospective study.

Materials and Methods

1. **Place of study:** The present study was carried at the department of pathology in collaboration with the department of TB & Chest Diseases, Surgery, ENT, Oral Maxillofacial Surgery, Radio Therapy in our hospital.
2. **Design of study:** A diagnostic prospective& retrospective study.
3. **Duration of study:** 1 year
4. **Sample size:** Total 50 cases.
5. **Sample types:** Histopathological specimens received in respective histopathology section of the pathology department after any chemotherapy or radiotherapy.

Inclusion criteria

- Histopathological specimens, includes specimen having multiple tissue bits (crush material from lung), scanty tissue in biopsy material, mass excision biopsy and whole organ excision, received in respective histopathology section of the pathology department after chemotherapy or radiotherapy.
- Specimens was sent to the histopathology section were fixed, processed, stained with H&E and was reported.

Exclusion criteria

- All Pre-therapy sample received in respective section were excluded from the study.
- Histopathological specimens with poorly fixed in formalin or very scant tissue material for interpretation.

Statistical Analysis

Descriptive statistics were used to determine histological findings. (As Mentioned in criteria for evaluation.)

Method

After collecting all investigations including radiological, previous histopathological or cytopathological and other laboratory tests to decide the stage of the cancer from concern clinicians or surgeons. Detailed histopathological examination was carried out especially looking for chemotherapy-induced or radiotherapy-induced histopathologic changes like necrosis, fibrosis, inflammatory reactions, and other retrogressive changes.

For carcinoma breast, neoadjuvant chemotherapy regimens, number of chemotherapy cycles varied from two to six depending on the initial size of the tumour to make them operable. The drugs and doses of neo-adjuvant chemotherapy given to the patient were recorded.

Criteria for evaluation

1. The tumour cells were evaluated for dissociation, dyscohesion, and loss of organization of the tumour cells and necrobiotic changes such as necrosis, vacuolation of nucleus and cytoplasm, karyorrhexis, pyknosis, and karyolysis. Any change in pattern or type of carcinoma was noted.
2. The stroma was examined for host response including fibrosis, elastosis, collagenization, and infiltration by lymphocytes, plasma cells, fibroblasts, histiocytes, and giant cell formation was observed. Similar changes in tumour cells and stroma were observed in the lymph nodes.
3. Epithelial-to-stromal ratio was calculated as the mean of readings in all sections and viable-to-nonviable tumour cell ratios were calculated in both pre-treatment biopsies and post chemotherapy specimens, viability being defined as distinct nuclear chromatin with intact nuclear and cytoplasmic membrane in the absence of the criteria of necrosis (karyorrhexis, karyolysis,

pyknosis).

4. Lymphocytic response was graded as: Grade 1, scattered lymphocytes between tumour cells; grade 2, formation of micro-aggregates of lymphocytes; grade 3, dense infiltration of lymphocytes destroying tumour cells or forming masses. The presence of lymphovascular embolization and in situ disease/cancerization of ducts were separately noted [5].

Result

The present study was conducted in the department of pathology with collaboration of the department of TB & Chest Diseases, Surgery, ENT, Oral Maxillofacial Surgery, Radiotherapy in our hospital.

Total 50 cases were studied, which includes specimen having multiple tissue bits (crush material from lung), scanty tissue in biopsy material, mass excision biopsy and whole organ excision. Sections were stained by H&E stain.

Table 1: Age and Gender distribution of cases (n=50)

Age in years	Male	Female	Total
01-20	00 (00%)	00 (00%)	00 (00%)
21-30	05 (10%)	02 (04%)	07 (14%)
31-40	04 (08%)	03 (06%)	07 (14%)
41-50	08 (16%)	06 (12%)	14 (28%)
51-60	05 (10%)	06 (12%)	11 (22%)
61-70	06 (12%)	03 (06%)	09 (18%)
71-80	02 (04%)	00 (00%)	02 (04%)
Total	30 (60%)	20 (40%)	50 (100%)

Above table shows most cases were from age group between 41-50 years and male: female ratio is 3:2.

Table 2: Tumour cells changes (n=50)

Site	Dissociation	Dyscohesion	Necrobiotic changes
Lymph node	13	10	12
Head & Neck	12	11	11
Breast	05	05	05
Liver	03	03	03
Lung	06	06	06
Anterior chest wall	09	08	08
Buccal mucosa	02	02	02
Total	50	45	47

Above table shows tumour cells showing dissociation, dyscohesion and necrobiotic changes after chemo or radiotherapy.

Table 3: Stromal changes (n=50)

Site	Fibrosis	Elastosis	Lymphocytic infiltration			
			Grade I	Grade II	Grade III	Total
Lymph node	10	06	00	08	02	10
Head & Neck	12	06	02	04	02	08
Breast	05	04	02	02	00	04
Liver	05	02	01	00	00	00
Lung	01	00	02	02	00	04
Anterior chest wall	09	03	02	01	00	03
Buccal mucosa	02	00	01	01	00	02
Total	25	21	10	18	04	32

Above table shows stromal changes after therapy in affected tissues and lymphocytic infiltration grading [5].

Grade I: Scattered lymphocytes or in between tumour cells

Grade II: Microaggregates of lymphocyte

Grade III: Dense lymphocytic infiltration.

Table 4: Nuclear features (n=50)

Site	Hyperchromasia	High N:C ratio	Prominent Nucleoli	Karyolysis/ Karyorrhexis
Lymph node	13	12	12	12
Head & Neck	12	11	09	09
Breast	05	05	05	02
Liver	03	02	03	00
Lung	06	06	06	03
Anterior chest wall	09	08	08	07
Buccal mucosa	02	02	02	00
Total	50	36	44	33

Above table shows various nuclear changes after therapy.

Discussion

In present study histopathological changes have been observed following neo-adjuvant therapy in individual tumors.

The present study was carried out on 50 patients in which the effects were divided mainly into two, as pathological changes in tumor cells and changes in the stroma. Though these changes have been observed by many workers, positive correlation of the presence of these changes with the effect on chemotherapy has been significant in many studies which we will discuss here.

1. **Histopathologic changes following neoadjuvant chemotherapy in various malignancies. Divyasethi *et al.* [5]:** Total 60 patients were included 40 patients with carcinoma breast and 20 patients with other malignancies who received neoadjuvant chemotherapy. Subgroup A- patient with initial pathologic material submitted as trucut or wedge biopsy and group B- lumpectomy specimens. In group A, total 47 cases in which 07 (14.9%) saw grade I, 16 (34%) saw grade II & 05 (10.6%) saw grade III lymphocytic infiltration and in stromal host response, elastosis/collagenisation was seen in 19 (52.7%) and stromal fibrinoid necrosis 03 (8.3%). In group B, total 20 cases in which 02 (10%) saw grade I, 06 (30%) saw grade II and 02 (10%) saw grade III lymphocytic infiltration and in stromal host response, elastosis/ collagenisation was seen in 10 (90.9%), which is quite comparable to our present study.
2. **Therapy-induced histopathological changes in various breast cancers: the changing role of pathology in breast cancer diagnosis and treatment. Shazimasheereen *et al.* [6]:** total 39 cases were evaluated in which nuclear hyperchromasia was seen in 34 (87.2%), high N:C ratio was seen in 33 (84.6%), prominent nucleoli were seen in 30 (76.9%) and karyolysis/karyorrhexis 23 (59), which is quite comparable to our present study.
3. **Evaluation of various nuclear cytological changes in normal buccal mucosa and peritumoral area in patients with oral squamous cell carcinoma receiving concomitant chemoradiotherapy – sadiaminhas *et al.* [7].**

Total 76 patients were evaluated for nuclear karyolysis or karyorrhexis using serial scrape smear before (09.2%) and after immediate exposure (27.6%) to neo adjuvant CCRT, at 17th day (100%) and at the end of treatment (100%), which is quite comparable to our present study.

Other changes less commonly described in the literature were periductal inflammatory infiltrate (ductulitis), lobular atrophy, ductal and lobular atypia [8].

A change to either a higher or lower grade was noted by Rasbridge *et al.* [9]. However, no post-chemotherapy change in tumor grade was seen by Gazet *et al.* [10].

In the present study, the most common type was ductal carcinoma NOS; mucinous change appeared in three patients after chemotherapy who were diagnosed with ductal carcinoma NOS type in the initial biopsy

Tumor replacement by loose fibrosis is the most common pathologic event. In most cases, the intensity of fibrotic change is proportional to the degree of clinical-mammographic reduction of the tumor mass. However, some discrepancies exist in the sense of absence of microscopic changes in cases of well-documented mammographic reduction as well as in cases without clinical reduction but with large areas of chemotherapy-related fibrosis. The presence of pathologic response is significantly associated with better survival rate [11].

A meticulous gross examination of post-chemotherapy breast excision specimens is required with ample sectioning to identify the small foci of residual tumor. The pathologist should be aware of the possible nuclear and cytoplasmic changes of chemotherapy. Special stains may be required to confirm the nature of atypical scattered individual cells. Grading of post-chemotherapy breast carcinoma may not be a prognostic indicator, due to the cytomorphologic changes in the tumor cells [12].

Multiagent chemotherapy is often used to treat patients with locally advanced infiltrating breast carcinoma before mastectomy. One of the most important prognostic factors, histologic grade, may be altered by induction chemotherapy. Because locally advanced infiltrating breast carcinomas are frequently diagnosed by fine-needle aspiration, histologic grade can be determined in the mastectomy specimens only after chemotherapy [12].

Response efficiency to a new therapeutic agent can be assessed because it is easy to detect a treatment response in a relatively short time period. In this respect, many clinical trials have been designed to evaluate NAT. Patients with large cancers who show a response to NAT can undergo breast-conservation surgery. The degree of response to NAT can play a role as a prognostic factor. Given the potential benefits, exact assessment of breast specimens after NAT is very important.

In principle, the method to evaluate histologic subtype and tumor grade in breast cancer patients who received NAT is the same as that used for patients with non-neoadjuvant cancer. However, it is necessary to consider that NAT can affect histologic architecture, nuclear features, and tumor mitosis. Thus, some cases require comparison with pre-treatment biopsy findings

Conclusion

Various histopathological changes have been observed following neo adjuvant therapy in individual tumors in this study. Various nuclear abnormalities reveal a statistically significant increase with increasing chemo/radiation doses and time interval.

Persistence of dysplastic and malignant cells from peri-tumoural area during and at end of this treatment can be a sign of resistant or recurrent carcinoma.

The tumor grade decreases and differentiation improves, in addition to the retrogressive changes and increase in stromal component, as a result of therapy in carcinoma breast as well as in other malignancies.

The results of this study again reveal that the response to therapy may be markedly variable in patients. The desired response in some may be achieved with a fewer number of cycles, whereas in other patients, the tumor may resist even with the maximum number of neo-adjuvant therapy cycles presently employed, thus defeating the very purpose even at the potential risk of toxicity.

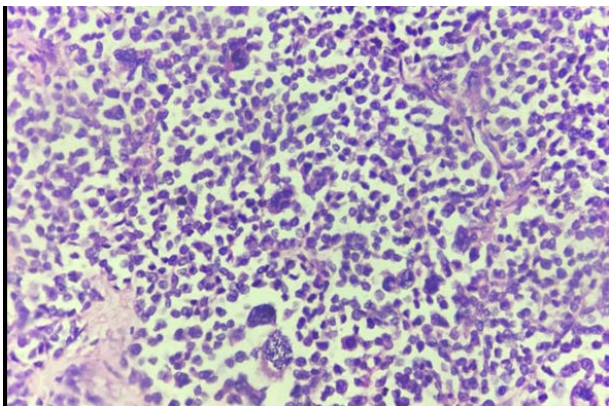

Fig 1: Section from anterior axillary swelling shows pleomorphic malignant cells, nyclear pleomorphism and scant cytoplasm with lymphocytic infiltration in known case of ducatl carcinoma breast post chemotherapy (H & E 10x)

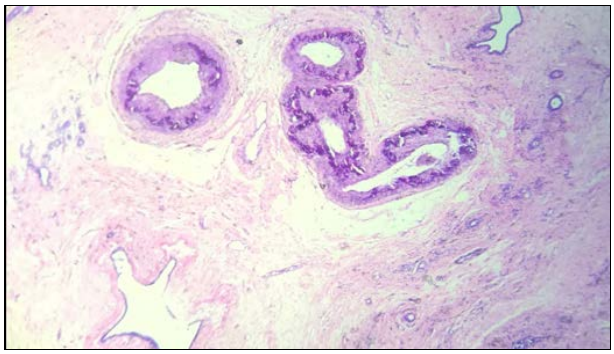

Fig 2: Section from breast tissue shows elastosis in a known case of ductal carcinoma breast post chemotherapy – stromal reaction. (H & E 10x)

Limitation: Our study had smaller sample size, so certain observation cannot be generalised & larger cohort study is required to support our findings.

Conflict of Interest
Not available

Financial Support
Not available

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