A Radio-Pathologic Atlas of Breast Diseases

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Edited by

Shinya Tajima, Ichiro Maeda
and Shinichi Tsuchiya

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*I dedicate this book for my family, Mina Maruoka-Tajima, Eiji Tajima, Shigeyasu Tajima, Yasu Tajima, Isematsu Tajima and Professor Junki Koike.

(Shinya Tajima)

*I dedicate this book to my father Reiichi, my mother Sada, my wife Atsuko, my daughters Kyoko and Hiroko, and my son Junichi.

(Shinichi Tsuchiya)

*I dedicate this book to my wife Katsura Maeda, my children Taichi, Mei, Ukai and Moi, my father Kazuhiko, my mother Reiko, and my ancestors Yasutami Yamaguchi and Setsuko Yamaguchi.

(Ichiro Maeda)

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PREFACE

It is said that one person in every eleven is diagnosed with breast cancer in Japan, and breast cancer is a life-threatening disease across the world. Hence, early detection of breast cancer is thought to be important, and it is thought that the combination of mammography and ultrasonography in screening could detect breast cancer in more than 90% of cases. We edited a book entitled *A Radio-Pathologic Atlas of Breast Diseases*, which aims to the primary handbook of mammography and ultrasonography in speculating pathology. We want graduate students of radiology, breast surgery and pathology to use this book. Basic breast pathology is important for graduate students because speculating on a histological subtype when diagnosing mammography and ultrasonography is important. In diagnosing breast mammography and ultrasonography, knowing the pathological structure is critical because the convalescence changes according to the pathological subtypes.

Our book details both benign and malignant lesions of radio-pathological correlation. To the best of our knowledge, this type of book is rare. This book therefore has the potential to be the Bible for graduate students of radiology, breast surgery and pathology. Furthermore, we emphasise the radio-pathological correlation of comparing ultrasonography to pathological gross findings. Hence, it could clarify the correlation of ultrasonographical images and naked-eye images. We can also speculate the histological subtype when we diagnose the mammography and ultrasonography. We think this point is one of the advantages of this book.

This book consists of three chapters. The first is about the basic pathology of the breast structure of a normal mammary gland, such as breast lobule, lactiferous duct, mammary stroma and so on. Changes of the breast tissue through aging are also depicted.

In chapter two we introduce basic histological subtypes of breast diseases containing both benign and malignant lesions, which allows us to reference the histological subtypes in daily pathological diagnoses.

In chapter three we introduce thirty-five cases of radio-pathological correlation. This chapter is the most important to the practice volume and topics. In this, we consider pathological diagnoses from mammography and ultrasonography. On the left-hand page we arrange the images of mammography and ultrasonography; on the right we arrange the answers of gross pathological and histological findings. This is important for keeping an open mind in speculating on the histological subtype. The malignant epithelial tumour is the most important aspect because diagnosing malignancy is

important in daily practice. Besides this, we introduce the cases of confusing types as examples of a pitfall, as we have to pay attention to the subtle changes in mammography and ultrasonography.

I hope this book will be a Bible for those working in breast diagnosis and treatment, and I sincerely thank Cambridge Scholars Publishing for its publication.

Shinya Tajima MD, PhD
St. Marianna University School of Medicine Department of Pathology and Radiology

INTRODUCTION

I am deeply grateful for the continuing collections of many case studies in the writing of this book. I am fortunate to have my own circumstances.

As a doctor, I am a part of the modern day while I have also inherited the successive DNA (identity) that has been inherited from time to time.

Advances in modern science and modern technology have made the ultrasound image clearer, and the door to the world of pathology that was wrapped in a veil has been opened wide.

Due to the increased consistency of ultrasound images, macroscopic morphology and pathological tissue images, the need has arisen to further enhance the collaboration between clinicians, radiologists, medical radiology technologies, pathologists and pathological examination technicians.

I hope this book will be a bridge between those occupations and help you deepen your knowledge of breast pathology from various perspectives.

I would like to express my gratitude and reverence to Dr. Shinichi Tsuchiya (Professor at Nippon Medical School Hospital and Visiting Professor at St. Marianna University School of Medicine) for giving me such an opportunity, and I express deep gratitude to Dr. Futoshi Akiyama (Pathology of Japanese Foundation for Cancer Research), who taught me many expertise in breast pathology.

To the doctors of the breast pathology study group, Japan breast pathology diagnosis cram school: thank you for allowing the scales to fall from me eyes several times, for which I express my appreciation.

I also express my sincere gratitude to my former professor Dr. Mamoru Tadokoro, Dr. Hideo Atari and Dr. Masayuki Takagi for teaching me the fundamentals of diagnostic pathology, Professor Mamoru Fukuda for writing an excessive recommendation letter, the breast and endocrine surgeon Professor Yasuo Nakajima, the radiologist Professor Shinji Yamaguchi and the staff of the former First Department of Surgery.

I would like to express my deepest appreciation to the secretaries and the staff of the Department of Pathology at St. Marianna University Hospital and the clinical specialist of St. Marianna University School of Medicine department of diagnostic pathology, who consistently produce high-quality specimens.

Finally, I would like to express my sincere gratitude to Cambridge Scholars Publishing for the publication of this book.

Ichiro Maeda, MD, PhD
Department of Pathology, Kitasato Institute Hospital

INTRODUCTION OF SUPERVISION

The prevalence rate of breast cancer in Japan occupies the top ranking of women, and the number of deaths continues to increase.

Compared to Europe and the United States, the low examination rate is one of the reasons for this, and it is inevitable that improvement of the examination system is required. Currently, the resolution of images obtained from digital mammography and ultrasonic examination equipment has dramatically improved, making it possible to capture smaller lesions (especially non-invasive carcinoma), but in order to make a definite diagnosis, pathological diagnosis is necessary. However, the pathological feature of the breast is varied, and it is rare that it shows the same morphology even for breast cancer. Pathologists have hesitated to diagnose benign and malignant, and in some cases they have to decide that these are “difficult to distinguish.”

Estimation of tissue type using image diagnosis is extremely effective as one solution. That is, image diagnosis and pathological diagnosis are considered to be complementary and reversible at the same time. If clinicians, pathologists, radiologists, clinical laboratory technicians and medical radiology technicians cooperate to make an accurate as possible diagnosis, the number of cases judged to be “difficult to distinguish” will decrease: we expect that we can approach zero.

In chapter one of this book we outline the basic structure of the breast, and in the case review of chapter three we devised what kind of tissues/cells are depicted by mammography and ultrasonography so that you can identify them at a glance. Presenting mammography images, ultrasound images and histopathological images of commonly seen diseases while comparing them has a sense of reality similar to a breast disease conference.

Surgeons and radiologists will be able to improve diagnostic imaging by knowing the background of the tissue diagnosis and even the reflections of staff members who did the examination, so you can see whether you are doing the same thing. For example, we can compare how the form of calcification is reflected in the histology, which we believe can be fed back for future examination. Since image diagnosis has the characteristic of displaying each component constituting a lesion, the proposition that the pathological feature of the lesion is clarified is the aim of the author.

As this book has such a wide range, it will help clinicians to select a more accurate treatment, and I believe that the inspection staff can also contribute to further improvements in inspection technology.

Finally, I would like to thank Professor Yasuo Nakajima, Dr. Yoshihide Kanemaki and Dr. Hiroko Okazaki (Department of Radiology, St. Marianna University) for the

writing and cooperation on mammography and ultrasound findings, and I would like to express my deep appreciation to Cambridge Scholars Publishing for publishing this book.

Shinichi Tsuchiya, MD, PhD
Assistant Director of the Iida Hospital in Nagano
Professor of St. Marianna University School of Medicine

RECOMMENDATION

I reread the old book *Clinical Pathology Breast Cancer Tumor Graphic Diagram* (Kurume Masaru, 1960, Nakayama Bookstore) after many years. The preface of this book has the following description:

> Although the only symptom that is always seen in breast cancer is a mass, there are few cases when making a tumor or induration in the breast, including pregnancy and lactation, some of which are clearly related to the occurrence of breast cancer. Differentiation from breast cancer is extremely important in that hardening in the breast forms the only symptom. Differentiation between these diseases and breast cancer can be done in various ways. In most cases, it is necessary to have a histopathological examination.

For the past 50 years, breast cancer treatment has greatly advanced. During this period, breast pathology advances and its importance has been increasing year by year. Unlike 50 years ago, a definite diagnosis of breast cancer by a method other than pathological diagnosis was not possible. On the contrary, the pathological diagnosis of breast cancer becomes difficult as the number of early breast cancer increases, and a pathologist with outstanding diagnostic ability is needed to discriminate between DCIS, LCIS, ADH, ALH and the like. In addition, rapid, accurate and precise pathological diagnosis is required for breast-conserving surgery and sentinel lymph node biopsy. In addition, the treatment means of systemic therapy has been determined by various pathological findings. That is, it can be said that "treatment of breast cancer is only established when accurate pathological diagnosis is guaranteed."

Ichiro Maeda, Shinichi Tsuchiya and Shinya Tajima, the editors of this book, are pathologists driving the breast pathology of Japan into the future. In the book written by the newly developed pathologists, there are likely to be many immunostaining and molecular biology descriptions, but this book sticks to the findings of HE staining, which is the basis of breast pathology to the last. The spirit of the authors who value this basic is the same as that of the predecessors who developed breast cancer medical treatment in Japan, and it is impressive. The feature of this book is that you can understand the basics of breast pathology naturally as you read the pathological descriptions written in easy-to-understand words. In the book, the authors state that "pathological specimens have few opportunities for clinicians to see, but please readily observe HE stained specimens." Medical professionals engaged in breast cancer practice should read this book and have opportunities to see HE specimens with

pathologists. Knowledge of breast pathology is reflected in the improvement of clinical ability in the present. The second part of this book is a comparison of pathology and images using cases. Again, the authors compare pathology with mammography and ultrasound images, which are the basis of breast images, rather than MRI and CT. By comparing beautiful images of tissues, basic breast diagnostic ability is improved. Besides, by seeing the histopathological image and unravelling the findings, you can enjoy the excitement and fun of film reading at academic societies. Breast cancer is the first cancer resulting from age-adjusted incidence. The number of deaths in breast cancer have increased in the world. For the medical treatment of what has become a big social problem, I am praying for the further development of the authors as some of the few breast pathologists in our country.

Mamoru Fukuda, MD, PhD, President of Breast and Imaging center,
St. Marianna University.

CHAPTER ONE

GENERAL INTRODUCTION

SHINYA TAJIMA, ICHIRO MAEDA, SHINICHI TSUCHIYA,
MOTOHIRO CHOSOKABE, KEIKO KISHIMOTO,
KOICHIRO TSUGAWA AND MASAYUKI TAKAGI

1: Basic Structure of the Mammary Gland

Section 1: Normal mammary gland

The mammary gland is one of the accessory organs (glands) of the skin, together with the eccrine sweat glands, apocrine sweat glands, and sebaceous glands. Unlike other skin glands, the mammary gland consists of both glandular and stromal tissue. The gland itself is surrounded by subdermal adipose tissue and is supported by Cooper's ligaments attached to the dermis. As the female individual matures, mammary glands increase in volume to form breasts.

The mammary gland comprises 15–25 mammary ducts opening at the nipple and branching inwards in a tree-like pattern. Each part of the mammary gland has its own name: mammary ducts start from the nipple openings and branch into interlobular ducts, which in turn split into extralobular terminal ducts, then intralobular terminal ducts and finally terminal ductules (Fig. 1). The nipple openings of the mammary ducts are lined by stratified squamous epithelium, which immediately changes to columnar epithelium inward from the nipple. A slightly expanded region called the lactiferous sinus is also present behind the nipple. The lactiferous sinus is markedly smaller in humans than in cattle, in which it is thought to serve as a storage site for milk. Its function in humans is unclear. The extralobular terminal duct, intralobular terminal duct and terminal ductules together form the terminal duct lobular unit (TDLU). In addition to being a hormone-sensitive site, the TDLU is also said to be the site of origin of the majority of mammary gland lesions, including breast cancers.

The epithelium of the mammary gland (from mammary ducts to terminal ductules) consists of two types of cells: glandular epithelial cells, and myoepithelial cells. Glandular

epithelial cells are the cuboid to columnar cells responsible for milk production. Myoepithelial cells are small, flat cells that surround the glandular epithelial cells in a mesh-like pattern and contract to excrete milk from the nipple. This configuration of cell types is often referred to as two-layer structure, but in this book the term "two-cell pattern" is used, reflecting the fact that glandular epithelial cells and myoepithelial cells are different shapes. Dark bluish-purple lobular structures and pink stroma can be seen with hematoxylin-eosin (HE) staining at medium magnification view (Fig. 1), and individual lobules can be seen with HE staining at high magnification view (Fig. 2). The glandular epithelial cells and myoepithelial cells that make up the terminal ductules can be seen together with interlobular stroma, which in this case is a paler pink than normal stroma. This pale pink represents edematous or myxomatous degeneration. In immunohistochemical staining of alpha-smooth muscle actin (α-SMA) (Fig. 3), p63 (Fig. 4), myoepithelial cells are stained brown. This staining clearly shows the two-cell pattern of glandular epithelial cells and myoepithelial cells. Because invasive carcinomas disrupt the myoepithelial cell layer in addition to invading the stroma, this state is described as "loss of the two-cell pattern".

The components of mammary gland stroma include collagen fibres and adipose tissue, collagen-producing fibroblasts, fibrocytes, vessels (blood vessels and lymph ducts), elastic fibres, smooth muscle and blood components such as erythrocytes, leukocytes and lymphocytes.

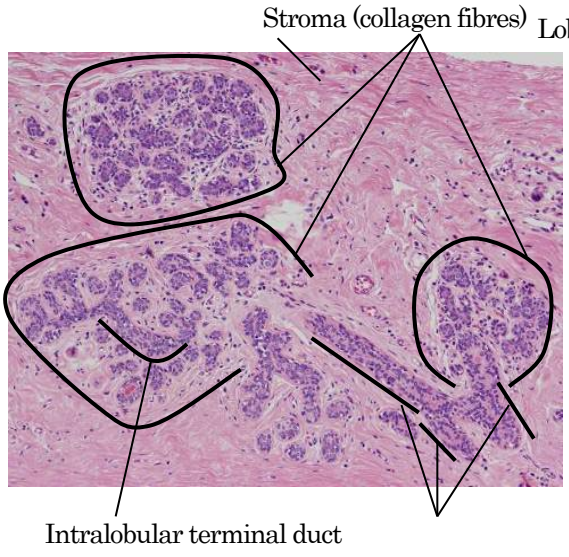


Fig. 1

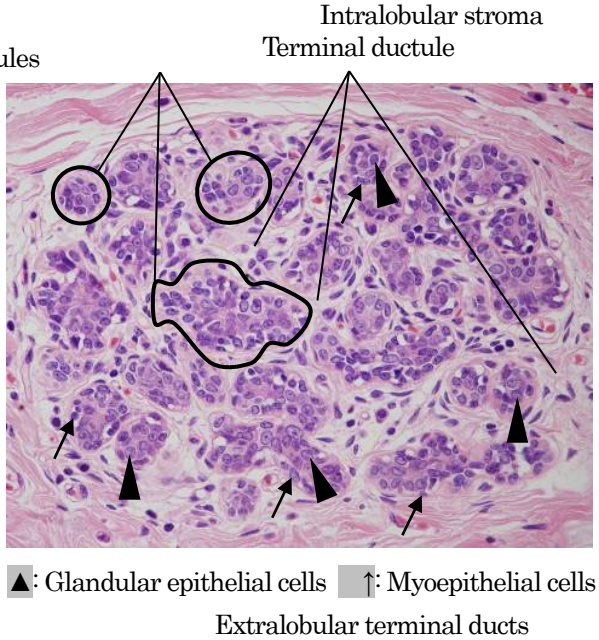
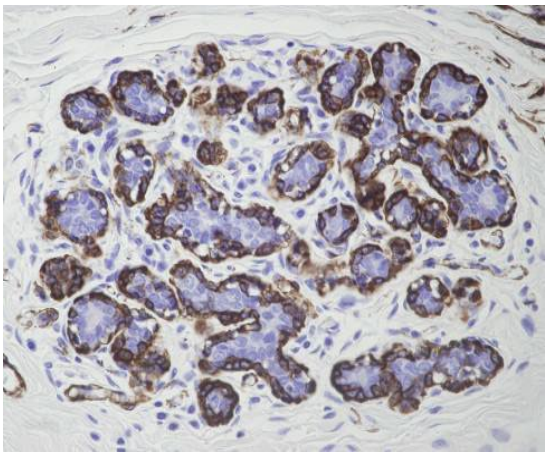
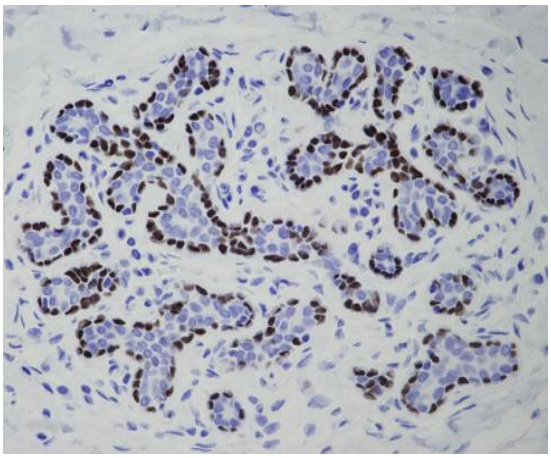


Fig. 2



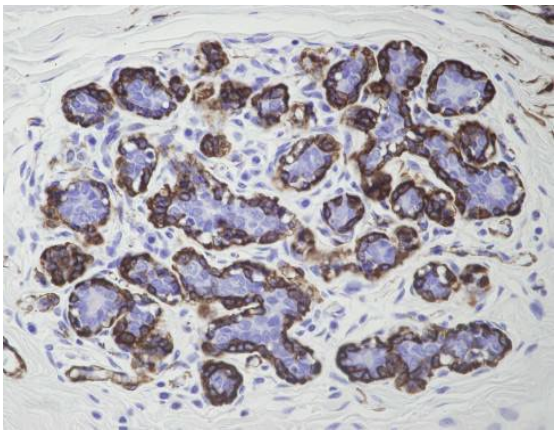
a-SMA: Immunohistochemical stain (DAB staining)
Myoepithelial cell cytoplasm stains positive (brown)

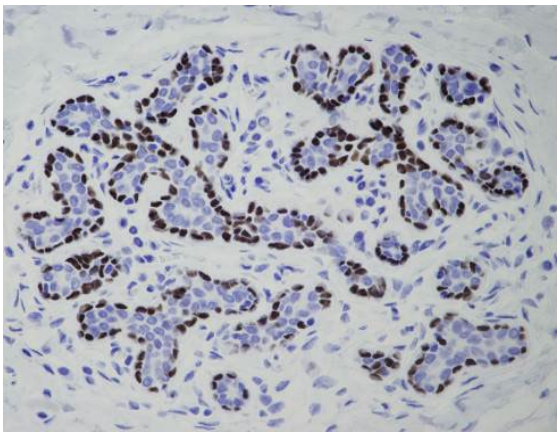
Fig. 3



p63: Immunohistochemical stain (DAB staining)
Myoepithelial cell nuclei stain positive (brown)

Fig. 4





p63: Immunohistochemical stain (DAB staining)
Myoepithelial cell nuclei stain positive (brown)

2. HE staining of mammary glands

Fig. 1 is a reverse grayscale (reversed black and white) image of a magnified macroscopic view of an HE-stained specimen (mammary gland). This technique creates an image resembling an ultrasound scan. Conversely, the HE stain can be thought of as a reversed black and white ultrasound image stained with colour (Fig. 2). Of course, pathological specimens are observed at higher resolution, but it is important to remember that the object being observed is still the same breast, whether by ultrasonography, mammography, CT or MRI. Clinicians do not often have the opportunity to see pathological specimens, so the reader should take time to examine this HE-stained specimen.

Hematoxylin and eosin staining (shortened to H&E stain or HE stain) is a double stain comprising hematoxylin (which selectively stains nuclei) and eosin. Unlike other characteristic stains that selectively colour specific substances, the HE staining provides adequate information in a histological section, and is the simplest and most information-rich

staining method.

To understand HE stainings of the mammary gland, a good grasp of the mammary gland structure and components described above is crucial. Mammary gland tissue includes epithelium and stroma. The epithelium consists of glandular epithelial cells and myoepithelial cells, whereas the stroma includes collagen fibres and adipose tissue, collagen-producing fibroblasts, fibrocytes, vessels (blood vessels and lymph ducts), elastic fibres, smooth muscle and blood components such as erythrocytes, leukocytes and lymphocytes. When observing HE-stained mammary gland, the most important features are: (1) epithelial cells (glandular epithelial cells and myoepithelial cells); (2) adipose tissue; (3) collagen fibres; (4) fibroblasts; (5) vessels; and (6) blood components, particularly leukocytes and lymphocytes. Structures in HE-stained specimens typically appear bluish-purple or pink. Nuclei are stained bluish-purple by hematoxylin, and the nuclei of (1), (4) and (6), and of the vascular endothelium of (5), are thus bluish-purple. Pink (eosin stain) mainly indicates the cytoplasm of (3) and (4). Adipose tissue (2) does not stain because the fat is dissolved away by alcohol during the preparation of histological sections. Under low magnification view, HE-stained sections consist almost entirely of pink and transparent areas, with some bluish-purple structures (Fig. 2).

The magnified image (Fig. 2) can be compared against the cross-section of a resected specimen (Fig. 3). Moving from the body surface inwards we can see the epidermis (bluish-purple: nuclei of stratified squamous epithelium), dermis (abundant collagen fibres coloured pink), subcutaneous adipose tissue (transparent), mammary gland tissue (pink, some bluish-purple) and adipose tissue (transparent).

The staining properties of stromal tissue differ depending on various factors. For example, stroma can be normal (Fig. 4), show edematous changes (Fig. 5), or be heavily infiltrated by inflammatory cells (Fig. 6).

Keeping these principles in mind when looking at lesions, cancer cells will begin to stand out clearly when viewing specimens such as invasive ductal carcinoma.

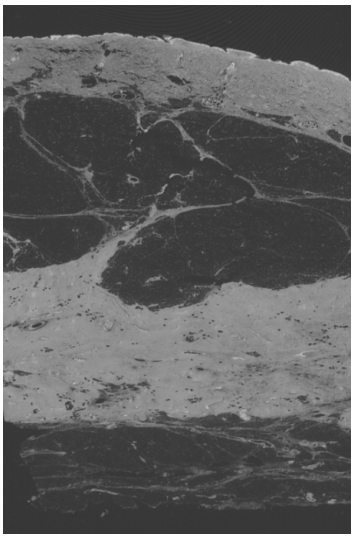


Fig. 1

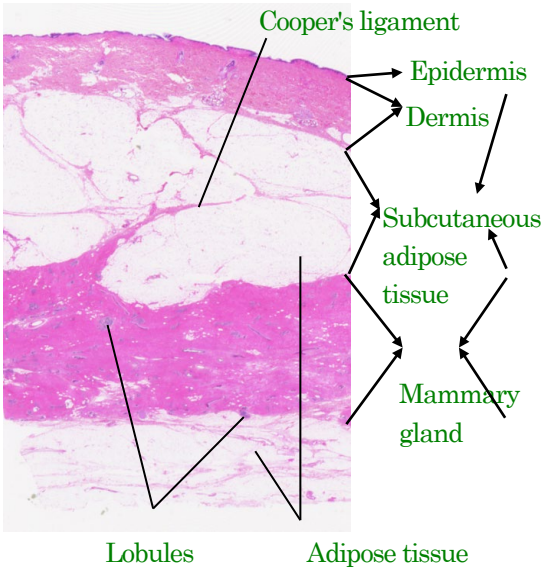


Fig. 2 Magnified HE stain

Fig. 3 Macroscopic view

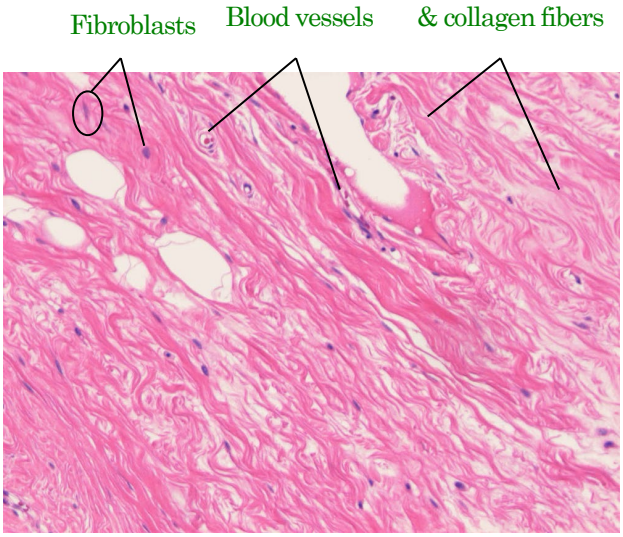


Fig. 4 Normal stroma

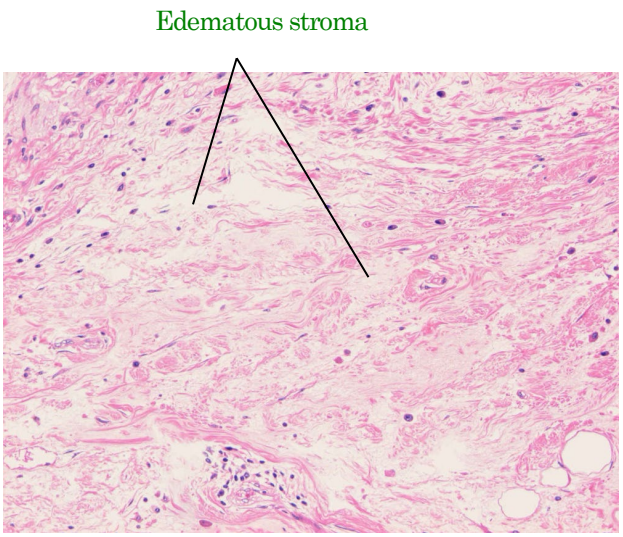


Fig. 5 Edematous stroma

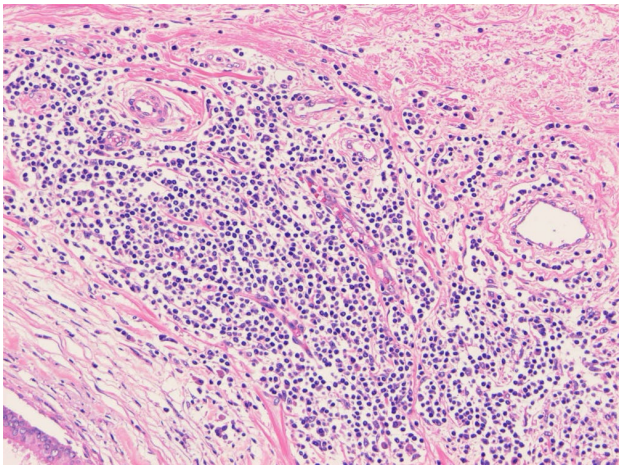


Fig. 6 Stroma with heavy infiltration of inflammatory cells

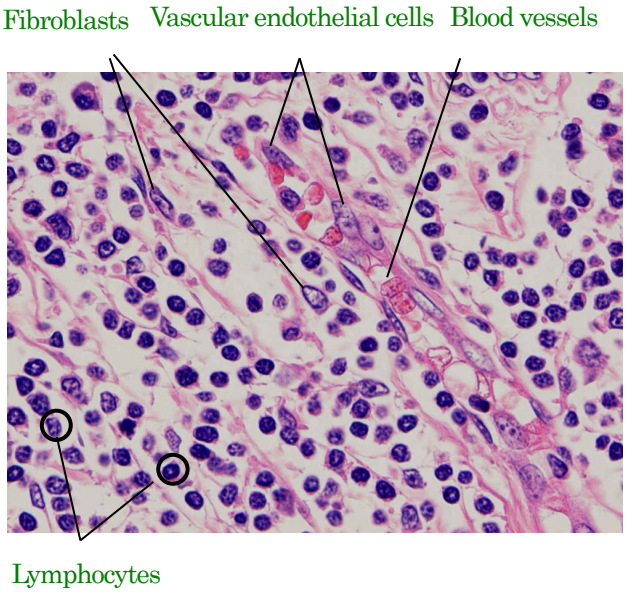
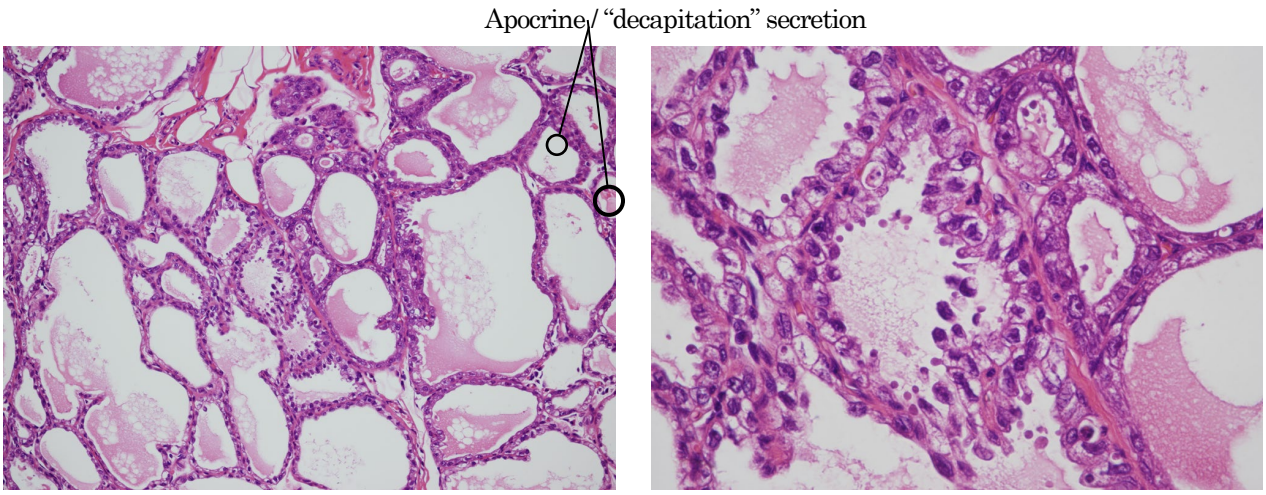


Fig. 7 High-magnification view of Fig. 6

3. Mammary gland during lactation

Preparation for milk secretion begins in the second trimester of pregnancy. First, the growth of terminal ductules occurs due to the influences of oestrogen and progesterone. In the third trimester, the terminal ductules fill with a milk-like secretion known as colostrum, which contains high levels of protein and fat. After birth, placental hormones decrease. At the same time, the pituitary hormone prolactin is secreted and milk secretion begins. After 2–3 days, the milk supply changes from colostrum to mature milk. In terms of histology, mammary gland tissue during lactation is characterised by the growth and expansion of terminal ductules to form the dominant structure, and a decrease in stromal components. Terminal ductules are lined with columnar and cuboid epithelial cells, and numerous balloon-like secretions can be seen projecting into the lumen.



HE stain: Medium magnification:
Mammary gland during lactation
Terminal ductules are expanded.

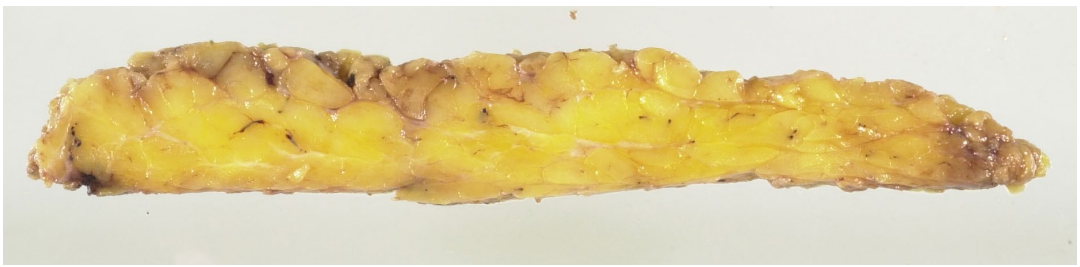
HE stain: High magnification:
Apocrine / "decapitation" secretion is visible in the terminal ductule.

4. Age-related changes

During infancy, mammary gland tissue remains undeveloped and is the same in boys and girls. When girls enter puberty, breasts form due to the influence of female hormones. Breast formation involves elongation and profuse branching of the mammary ducts, and the proliferation of adipocytes and fibrous connective tissue.

Atrophy of mammary gland tissue varies to a certain extent between individuals, but ageing is always accompanied by histological changes, including decreases in fibrous connective tissue, increases in fat, and atrophy or loss of terminal ductule epithelium.

Female in her 40s. Fibrous connective tissue is in good condition. No fatty changes are present.



Female in her 70s. Fibrous connective tissue has decreased and fatty changes are visible.

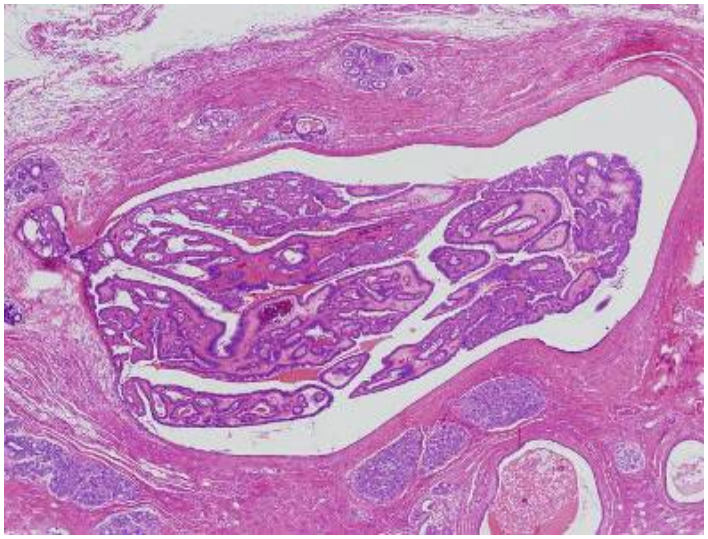
CHAPTER TWO

ITEMISED DISCUSSION

SHINYA TAJIMA, ICHIRO MAEDA, SHINICHI TSUCHIYA,
MOTOHIRO CHOSOKABE, KEIKO KISHIMOTO, KOICHIRO TSUGAWA
AND MASAYUKI TAKAGI

A Benign Epithelial Tumours

1. Intraductal papilloma



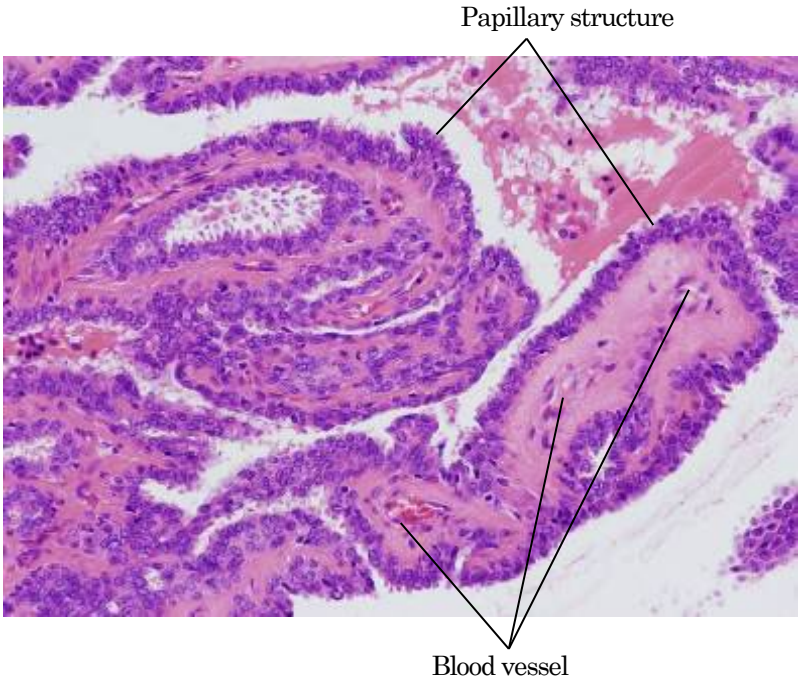
Intraductal papilloma, Low-power image

A papillary lesion is visible in a dilated duct.

Intraductal papillomas account for about 10% of benign mammary tumours, with the majority of cases in women in their 40s and 50s. Histologically, epithelium with an intact bilayer structure within a dilated duct undergoes papillary proliferation with accompanying stroma. If the duct is cystically dilated, the tumour is known as an intracystic papilloma. WHO classifies these tumours as central papillomas. Histologically, there are two papillary forms: the main type has a core of vascular connective tissue, and the other lacks stromal connective tissue.

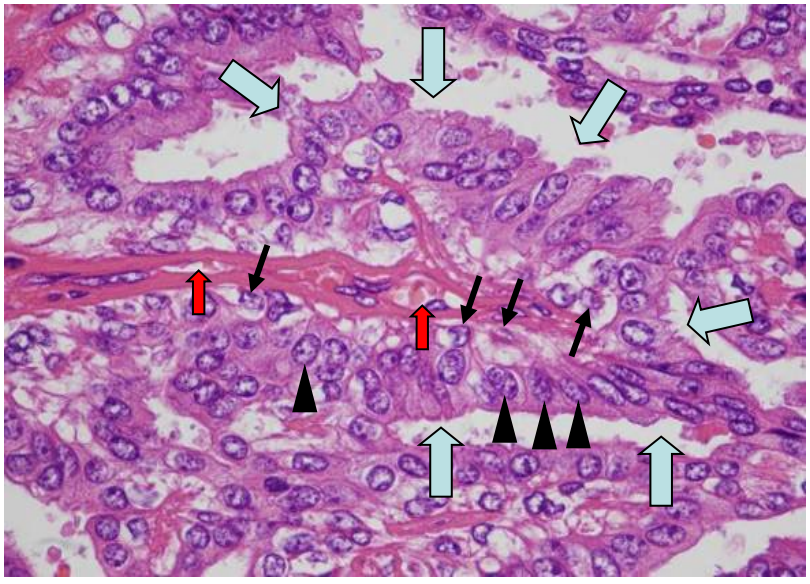
Clinically, intraductal papilloma may be accompanied by bloody nipple discharge and is often difficult to differentiate from cancer. On ultrasound, this tumour is often observed as a hyperechoic mass within a hypoechoic dilated duct.

Lesions that require histological differentiation include intracystic papillary carcinoma as a form of ductal carcinoma in situ, duct hyperplasia, and duct papillomatosis (corresponding to peripheral papilloma under the WHO classification). There is evidence that duct papillomatosis in particular may be associated with ductal carcinoma in situ. Intraductal papilloma and duct papillomatosis (or peripheral papilloma) must therefore be diagnosed as separate entities. Either way, this tumour presents challenges for pathological diagnosis in terms of identification as benign or malignant.



HE stain, medium-power image

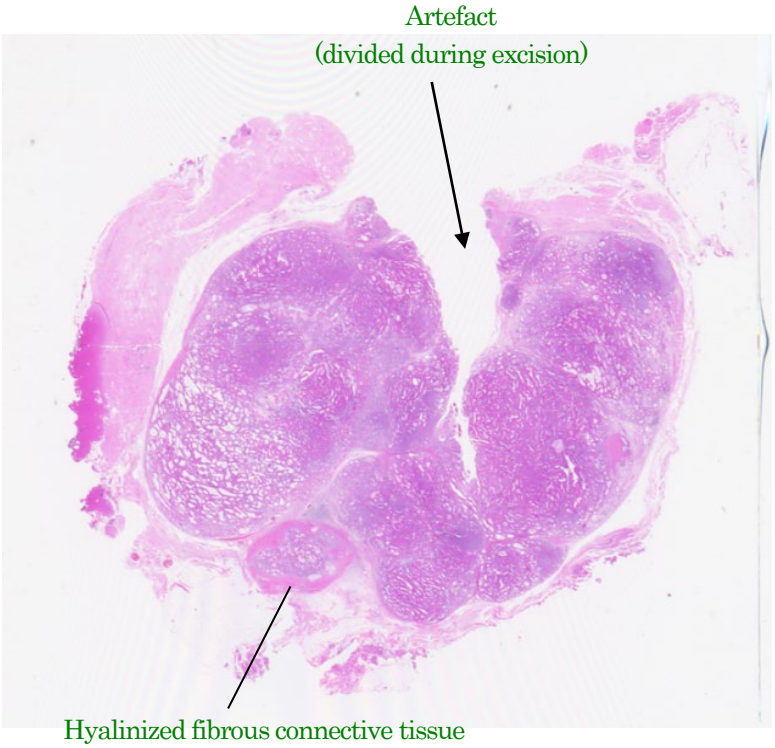
Papillary structures with a core of vascular stromal connective tissue.



HE stain, high-power image

Papillary structure with a core of vascular stromal connective tissue and an intact bilayer of glandular epithelial and myoepithelial cells.

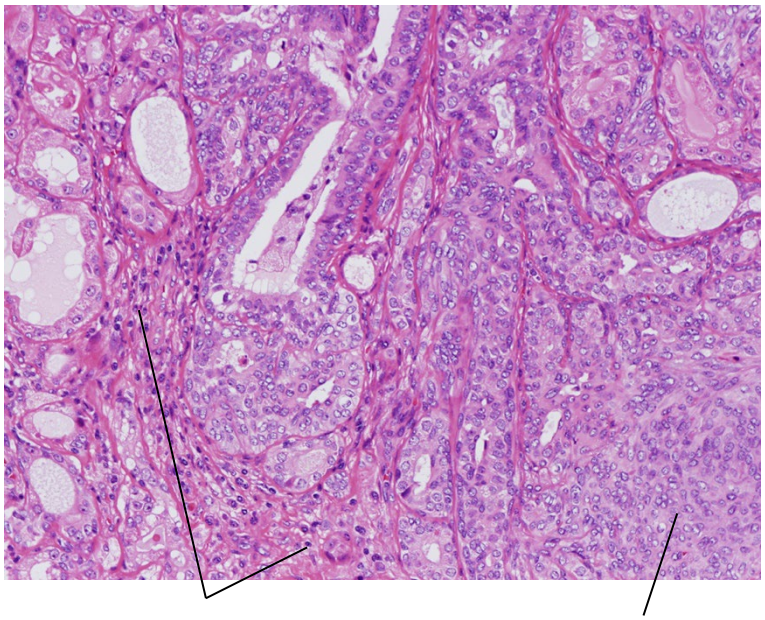
2. Ductal adenoma



HE stain, Loupe image

Lobular, well-defined tumour

Ductal adenoma can occur in women from their 20s to 70s, but is most common in those over the age of 40. WHO classifies this tumour under benign epithelial proliferations – adenomas. As reported by Azzopardi et al. (1984), and implied by that paper's subtitle, "A Lesion which Can Mimic Carcinoma," it is a benign tumour that is often difficult to differentiate from cancer. The tumour can have an irregular shape, and is sometimes diagnosed as malignant on mammography and ultrasound. Histologically, it consists of hyalinised fibrous connective tissue and a bilayer of epithelial cells, with epithelial proliferation completely filling the dilated duct. There may also be internal duct enlargement, pseudoinvasion or apocrine metaplasia, making it necessary to differentiate from invasive cancer and non-invasive apocrine ductal carcinoma (apocrine metaplasia in ductal adenoma may also have high-grade atypia).

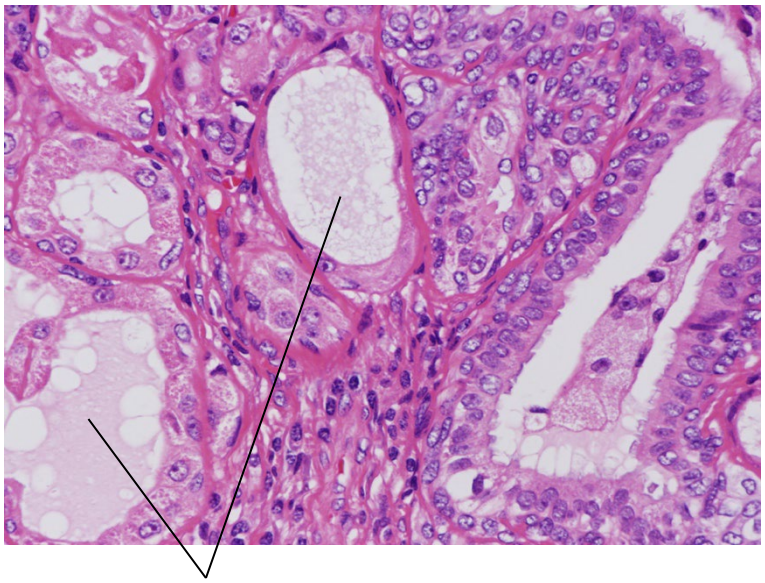


HE stain, medium-power image

This tumour consists of tubular ducts of various sizes and proliferation of collagen fibres. Proliferation of spindle-shaped cells presumed to be myoepithelial cells is visible in one region.

Collagen fibres with inflammatory cell infiltration

Proliferation of spindle-shaped cells

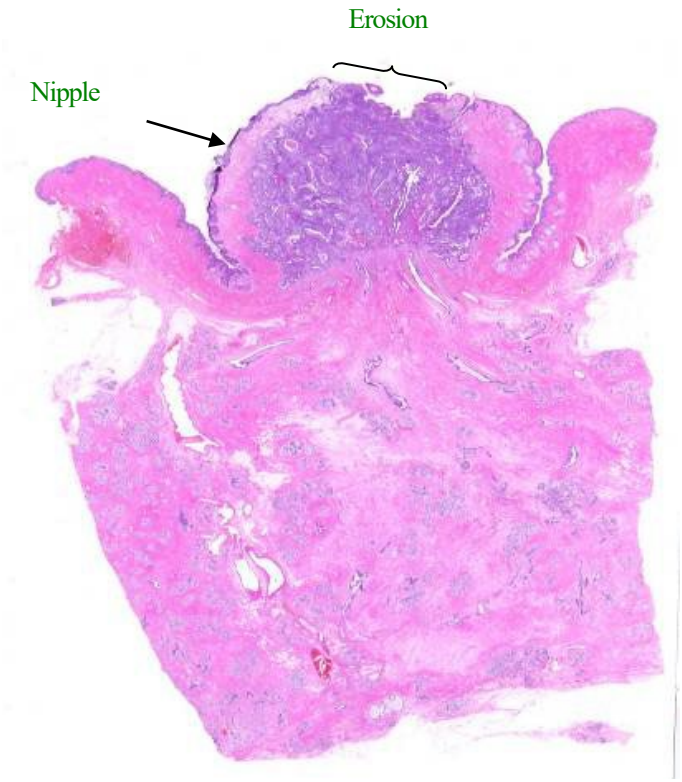


HE stain, high-power image

Ducts of various sizes with intact bilayer structure are visible, with apocrine metaplasia in places.

Ducts with apocrine metaplasia

3. Adenoma of the nipple



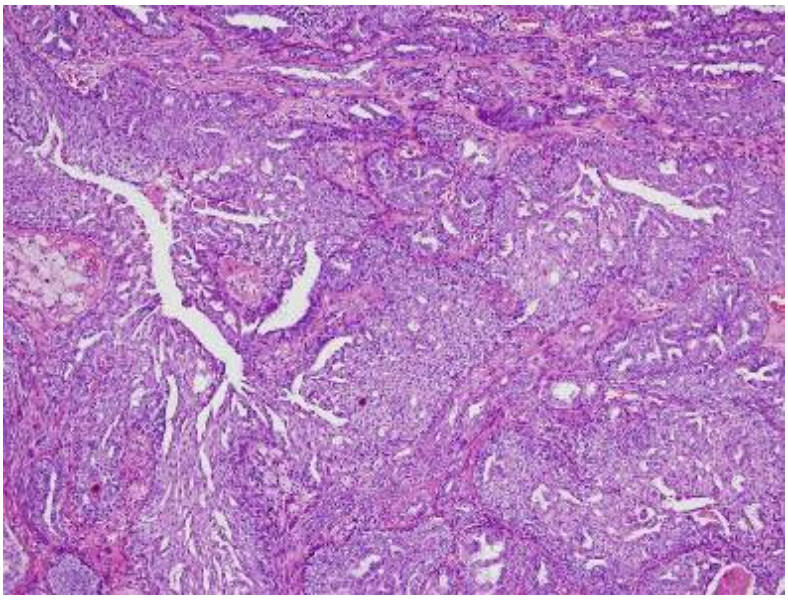
Adenoma of the nipple
Loupe image including nipple

The nipple shows erosion and a neoplastic lesion.

Although adenoma of the nipple is a comparatively rare, benign condition, it must be differentiated from Paget's disease and similar conditions. Its inclusion in textbooks and atlases is thus essential. It is also known as florid papillomatosis of the nipple, papillary adenoma of the nipple, nipple adenoma and subareolar duct papillomatosis.

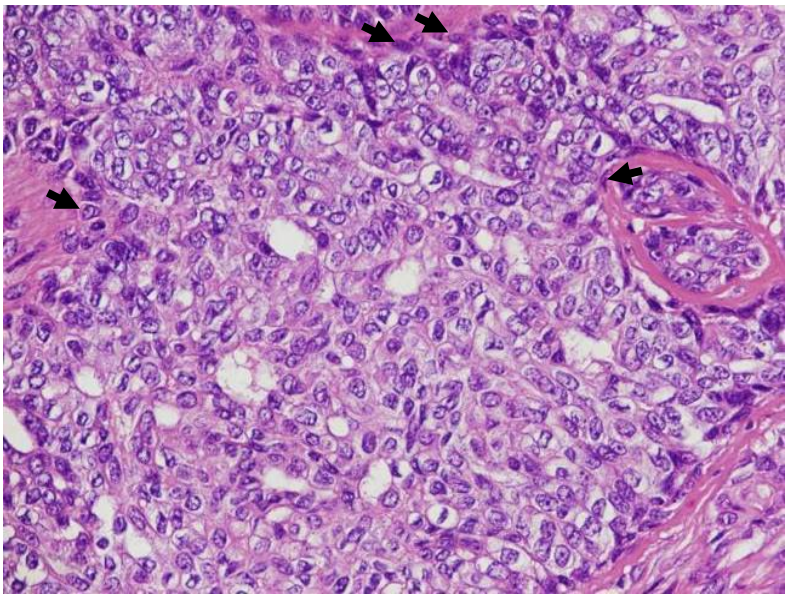
The clinical presentation often includes erosion of the nipple, nipple or sub-nipple induration, and abnormal nipple discharge. It should be differentiated from Paget's disease and breast cancer, but differentiation from breast cancer is most important from a histological perspective. The lesion is characterised by high-grade ductal hyperplasia with an intact bilayer structure, but it often presents as sclerosing adenosis-like pseudoinvasiveness, and may therefore be confused with solid tumour, papillotubular carcinoma, or ductal carcinoma in situ. Both clinically and histopathologically, this is a typical example of a benign lesion that is prone to overdiagnosis.

From a clinical and pathological perspective, if nipple erosion or nipple/sub-nipple induration is confirmed, a differential diagnosis that includes this disease is crucial. From a clinical perspective, the key point is to clarify for the pathologist whether the lesion site is the nipple or sub-nipple region. This information is useful in preventing overdiagnosis by the pathologist, and is arguably more significant than histology findings.



HE stain, medium-power image

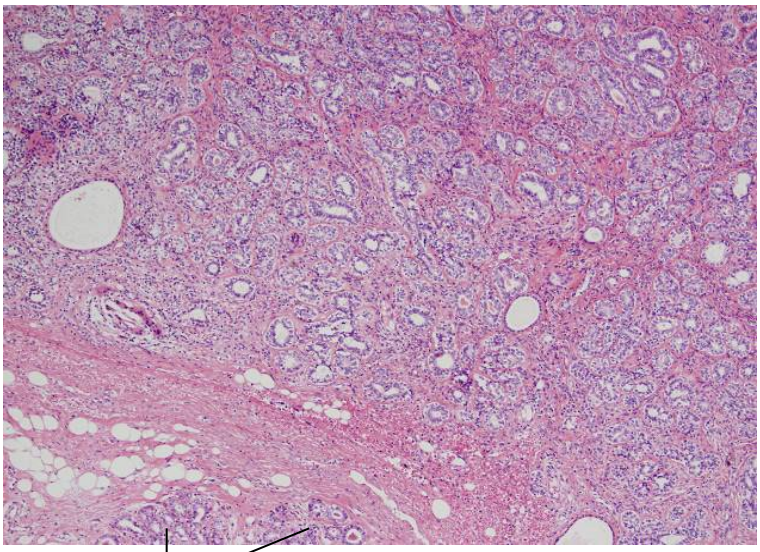
Lesion with papillary proliferation of intraductal glandular epithelial cells



HE stain, high-power image

There is marked proliferation of glandular epithelial cells, but myoepithelial cells (↑) are also visible, and the bilayer epithelial structure is intact.

4. Adenoma



Existing lobules

HE stain, low-power image
(Tubular adenoma)

Comparatively well-defined tumour (top)

The Japanese Society of Pathology definition of adenoma includes the subcategories of tubular adenoma and lactating adenoma.

Tubular adenoma tends to occur in young adults, but it is a very rare disease accounting for about 1% of benign tumours. The tumour is well-defined and must be differentiated from fibroadenoma (pericanalicular). Histologically, the epithelial component makes up a considerably high proportion of the tumour, and the structure is tubular or acinous.

Lactating adenoma is also rare, with onset during pregnancy or lactation. It has the appearance of a mammary gland during lactation and has a tubular or acinous structure. There is no conclusive evidence as to whether the tumour develops during pregnancy or whether it is an existing adenoma that takes on the appearance of a lactating mammary gland during pregnancy or lactation.