Volume 1

OUTLINE

CHAPTER 1

Introduction

Christopher D.M. Fletcher

In no area of anatomic pathology does the pathologist play a more important and crucial role than in the diagnosis of tumors. Although patients or laypersons are often entirely ignorant of this role and fondly imagine that their surgeon, other clinician, or oncologist is the true diagnostician—a misapprehension that some of our colleagues do not always dispel!—the reality is that the histology report is the principal determinant of diagnosis, likely clinical course, and therapy in any patient found to have a swelling or mass that proves to be neoplastic.

The need for timely, accurate, and detailed reports has never been greater, especially in our increasingly subspecialized profession and litigious society. This need comes at a time when the fields of tumor pathology and surgical pathology in general are expanding at an unprecedented rate, as reflected in the constant characterization of previously unrecognized tumor types or variants and the advancing delineation and application of new technologies that provide objective aids, not only to diagnosis but also to prognostication and the understanding of pathogenetic mechanisms which may enable novel therapies. This almost daily expansion in the surgical pathologist's database is manifest in the perceived need for ever more numerous journals and textbooks, which of themselves become increasingly more subspecialized—and revised and updated constantly. It is against this background that we have attempted to assemble a book dealing solely with the diagnostic histopathology of tumors in all organ systems, employing contributors who are all recognized specialists in their own areas of this field. I use the term *we* to underline the close nature of the collaboration among editor, contributors, and publisher in a project of this scale, but all errors and omissions, as in prior editions, are the sole responsibility of the editor. It should also be admitted that the rate at which surgical pathology is progressing will be reflected in the fact that some small parts of this book will inevitably be outdated or superseded by the time of publication.

The philosophy of this book has been to use the word *tumor* in its traditionally descriptive sense, in other words, to encompass neoplastic and, in some cases, nonneoplastic swellings. In this regard, it is commonly impossible, or at least a source of unresolved argument, to know whether certain lesions should be classified as hamartomatous, hyperplastic, or neoplastic; and most often, this text has adopted a pragmatically neutral role. It is of interest to note that currently no generally accepted definition of a neoplasm exists, because clonality alone is undoubtedly insufficient in this regard: Some processes traditionally regarded as reactive, for example in lymphoid tissue and synovium, have been shown to be clonal or oligoclonal. The capacity for growth in a transplanted (xenograft) model is perhaps the most convincing criterion but is not readily

applicable in a routine setting. Although the focus of this book is inevitably on histomorphology and associated ancillary tests, basic clinical data are also provided for most lesions, because these (most especially the natural history of a given disease) contribute significantly to accurate classification. The relevance of pathologic assessment in guiding treatment is also emphasized where appropriate. Guidelines to differential diagnosis (with appropriate cross-references where necessary) are described for those tumors that pose a particular or common problem.

This introductory chapter provides an opportunity to put forward, with due modesty, some personal approaches and views regarding the routine practice of diagnostic tumor pathology. The philosophy propounded hereinafter is individual and should not be construed as representing any policy agreed upon by the contributors. Some of the suggestions put forward undoubtedly are unoriginal but represent simply the folklore of surgical pathology passed down from great teachers in this field. In some quarters today the passage of such valuable information is regarded as being of little value; and we, as practicing histopathologists, are often encouraged to concentrate on purportedly more objective or scientific assessments of diagnosis or prognosis. This is reflected in the remarkable extent to which at least some of the content of large academic meetings worldwide is governed by fashionable but often transient techniques, antibodies, genes, pathways, or speculations. For as long as human tumors remain more varied, unpredictable, and idiosyncratic than their hosts, in terms of morphology, genomics, and behavior, a clear and unassailable need will exist for good surgical pathology based principally on careful and experienced light microscopic examination supported, where appropriate or necessary, by more modern techniques. For the time being at least, such skilled morphologic examination remains the gold standard in anatomic pathology, and it is unlikely to be surpassed in terms of either reliability or cost effectiveness in the near future, not least because genomic medicine has not as yet provided the simple answers that many had hoped for. Although it is true that some aspects of diagnostic pathology are subjective to a troubling degree, and although we should all work toward diagnostic reproducibility and objectivity by whichever means are most effective, it is a simple fact (at least in tumor medicine) that surgical pathology has never played a more important and pivotal role than at the present time. This is largely due to the central role of histopathologic parameters in determining therapy (at least for the majority of tumors) and hence the wish of clinicians to obtain (and often discuss) detailed pathology reports. The manner in which expertise in surgical pathology is often taken for granted in some academic centers, especially in Europe and the United States, is reprehensible and if it continues may lead to the progressive loss of important diagnostic skills because of erosion of experiential training and realignment of priorities in academic departments. In part this trend reflects an increasing tendency to shorten training time before certification, as well as the importance attached to grant raising by MD-PhDs and PhDs engaged in basic research, one outcome of which has been to widen the gap between much of the research undertaken in academic medical centers and the primary clinical mission of a hospital environment. A clear need exists for increased numbers of true physician scientists, increased funding for clinical and translational research, and greater mutual respect and collaboration between physicians and laboratory scientists. No one is better placed to take advantage of such collaborative opportunities than pathologists.

The guidelines that follow are set out in an order that corresponds, as far as possible, to the events in a surgical pathology laboratory from receipt of a specimen to the issuance of a report.

To diagnose a tumor in the absence of clear and complete clinical data is foolhardy, dangerous, and sometimes impossible. Many of our clinical colleagues often need to be reminded of this fact; even simple

information concerning age, sex, or location may be missing on the request form. This may raise compliance issues in addition to the potentially negative impact on patient care. If a specimen arrives in the laboratory without such data, then a medically qualified member of staff should not hesitate to contact the errant clinician or his or her staff; sometimes it may be appropriate to withhold the report until the pathologist is fully apprised of the necessary information. If a history of any previous neoplasm exists, especially at the same anatomic location, then the date of biopsy, diagnosis, and laboratory reference (when available) should be requested and recorded. If ancillary data such as the radiologic findings or serum chemistry in a bone tumor are necessary to make a diagnosis, then these should be requested, if not demanded!

Accurate and careful macroscopic description of a tumor specimen, particularly the definitive resection, is vital to diagnosis, prognosis, and retrospective data analysis for pathologic or clinical studies. The first occasion on which a resection specimen is examined in the pathology laboratory is usually the one and only time at which tumor size, weight, approximate extent of necrosis, and distance to resection margins can be gauged properly; once the specimen has been dissected, cut up, fixed in formalin, and otherwise distorted, then such valuable parameters often cannot be assessed. Similarly, features such as the type of margin (encapsulated, circumscribed, or infiltrative), the presence of satellite nodules, the presence (or involvement) of lymph nodes, and the extent of spread or invasion of adjacent structures are often best determined at the time of specimen dissection. The macroscopic description of the tumor in the final report should be sufficiently detailed to enable any other pathologist to conjure a clear mental image of the neoplasm. If this is done well, then often in combination with the clinical data it is possible to have a good idea of the final diagnosis, even before seeing the slides, especially in the more common tumor types. The other important role of good macroscopic examination is to ensure that a tumor is adequately sampled. The type or extent of sampling varies according to the size and anatomic location of the neoplasm, but as a general rule all lesions of appreciable size (perhaps >2 cm) should be sliced serially, and all areas showing a differing appearance should be examined histologically. In the appropriate organ systems, care should be taken to obtain blocks at the most likely site of muscular, serosal, or capsular invasion, as determined by naked-eye examination. Given the current prevailing fashion for inking specimen margins, I would like to make a plea in this regard—think before you ink! The indiscriminate inking of specimens, almost irrespective of type, has led in some contexts to the time-wasting and often irrelevant examination of margins in lesions that either have no potential to recur or have been so obviously marginally or incompletely excised that the positive (or at least oncologically inadequate) margins can be recorded grossly. In some cases, lesions (or biopsies) that are so small that they are embedded and sectioned in their entirety in one block are still inked, yet it is hardly a challenge to assess the margins (without inking) in such cases. This trend in specimen handling is almost anti-intellectual, often obliterates the benefit of examining a specimen in a thoughtful manner, and taints the validity of inking, which can be invaluable in an appropriate context.

Turning now to histologic evaluation, clearly this is a complex, often organ-specific process, the details of which are described in the separate chapters of this book. However, one or two pertinent generalizations can be made. Generalizations admittedly are dangerous and stand only to be shot down by exceptions to each rule; however, I believe they provide useful guidelines. In any patient with a previous primary (or recurrent) neoplasm, the slides should always be reviewed. This serves four main purposes: (1) It provides a simple but useful form of audit; (2) it enables comment to be made as to whether a tumor has advanced (or sometimes decreased) in histologic grade, thereby possibly influencing clinical outcome; (3) it is the only way of

determining with certainty whether a patient has developed two separate primary neoplasms, of the same or different types; and (4) sometimes such review provides a vital clue to diagnosis because recurrent or metastatic neoplasms, especially of mesenchymal type, show a remarkable capacity to alter their phenotype or to lose evidence of specific differentiation. What appears to be a weird or undiagnosable neoplasm, on occasion, can suddenly become a simple case when the previous histology is reviewed. In this regard, the principle of Occam's razor should be remembered: A patient is always more likely to have a single primary neoplasm with an odd pattern of recurrence than to have two distinct primaries.

A second generalization (although possibly a philosophical point I personally regard to be of paramount importance) is that, when possible, strict histologic criteria should be used for all tumor diagnoses. With rare exceptions, usually relating to specialist expertise based on experience, it is not acceptable to make an arbitrary diagnosis founded on personal whim. If a colleague or trainee asks how a diagnosis was reached, one should be able to enumerate reasons or criteria, be they positive or negative findings; hopefully, the days of saying "It is what it is because I say it is" are gone. The merits of this practice are that (1) uniformity in diagnosis is increased, thereby facilitating treatment decisions; (2) when analyzing published data or initiating new studies (whether clinical, pathologic, genetic, or genomic), one can ideally compare like with like—a vital step toward understanding tumor morphology and behavior, especially if large multicenter studies are required; and (3) the provision of clear diagnostic criteria is the only reliable means by which trainee pathologists can be taught. In this regard we need to introduce morphologic objectivity when possible, even though surgical pathology, by necessity, remains partly a subjective art.

The third, hopefully well-known generalization applicable to light microscopic examination of tumors using hematoxylin and eosin (H&E)–stained sections is that, in most (but not all) cases, low-power appearances often provide the best guide to the separation of benign from malignant lesions. Features such as the preservation of normal (often lobular) architecture, lesional symmetry, and the general impression of overall cellularity and nuclear atypia are exceedingly helpful in this distinction. Conversely, if one rushes straight to the high-power lenses, it is remarkably easy to find (and be misled by) cells with atypical or worrisome features in a very wide range of tumors or pseudoneoplastic lesions. Good examples of this phenomenon are the bizarre, often multinucleate stromal cells found in the submucosa or lamina propria of reactive, often polypoid lesions at almost any mucosal or cutaneous location and the densely hyperchromatic, irregular, degenerative (ancient) nuclei encountered in a variety of soft tissue neoplasms. Similarly, the presence of single or very rare abnormal mitotic figures need not equate with malignancy: I will always remember being shown such a mitosis in an otherwise normal proliferative endometrium during my first year in pathology!

With regard to the application of more modern techniques to diagnostic practice, this is mentioned (where relevant) in each chapter and key principles are discussed in greater detail in Chapter 31. Immunohistochemistry, now 40 years old, is indeed very useful but must always be interpreted in context. A seemingly aberrant result, especially if negative, should never be allowed to overrule an obvious morphologic diagnosis. Conversely, it should be recognized that the now quite widespread use of excessive antigen retrieval often leads to many confusing false-positive results—for example, in the early 2000s this was a notable problem in the use of CD117 positivity to accurately confirm a diagnosis of gastrointestinal stromal tumor. Quality control is vital if immunohistochemistry is to have a worthwhile role, and often this requires that any given laboratory should have a minimum throughput, albeit this required level of work activity remains poorly defined. Laboratories that perform a large number of immunostains on a daily basis

and do not change the staff around unnecessarily almost invariably produce more consistent and better quality results than their smaller, intermittently utilized counterparts. The value of using large antibody panels or complex algorithms for immunodiagnosis is somewhat controversial, but in these days of cost effectiveness it is my view that the choice of immunostains, where necessary, should be governed (and limited) by a carefully assessed differential diagnosis based on H&E morphology, through which specific questions need to be answered. The broader and more uncritical a panel of antibodies becomes, the greater is the likelihood of obtaining inexplicable, misleading, or aberrant results. Equally, if reliance is placed on an algorithm (especially one generated by a laboratory other than one's own), then a single aberrant or false-positive (or negative) result can lead to an irrational diagnosis, as well as a lengthy and costly trail of immunostains. A separate point of contemporary importance is the increasing trend of using immunohistochemistry or molecular testing for identification of potential therapeutic targets. Meaningful target identification and validation are important and expanding activities in pathology, but pathologists must not allow themselves to be bullied into undertaking such testing unless the protein or gene in question has first been proved to have biologic relevance (usually through activation or mutation) in the given tumor type and unless well-validated, reliable, and reproducible antibodies or well-validated mutational analyses are available for this purpose.

With regard to many of the more recent molecular genetic techniques, some of which undoubtedly have proved (and will continue to prove) to be valuable in tumor pathology, several points should be borne in mind. First, the published results concerning a pattern of gene sequencing, expression, or karyotypic abnormality in a given tumor type are only as meaningful (or as valid) as the corresponding morphologic diagnoses. If the diagnoses on which these results are based happen to be inconsistent or even wrong, then the conclusions made are often rendered worthless. Therefore collaboration and mutual respect between anatomic pathologists, molecular pathologists, and basic scientists are absolute prerequisites for continued progress in this setting. As expression profiling and sequencing technologies begin to allow rapid and detailed molecular profiling of large numbers of tumors, such professional interactions will be crucial in validating such data and in extracting maximal clinical value from this new information. The notion of treating a tumor blindly, based only on demonstration of a mutation or activated pathway, has as yet no proven validity; and basket trials to date have been a dismal failure. In this regard, it is also important to note that the majority of genomic profiling studies in recent years, trumpeting newfound diagnostic or prognostic accuracy, have failed (with a few notable exceptions) to improve on the daily achievements of routine light microscopic techniques. This may in part reflect the fact that many such studies have not included expert pathologists on the research team. Thus the second key point, despite initial optimism, is that many of the molecular and genetic parameters assessed in recent years, with important exceptions (e.g., N-myc amplification in neuroblastoma, cytogenetic and molecular characterization of many leukemias and sarcomas, detection of minimal residual disease in hematolymphoid neoplasms, and detection of therapeutically important mutations in certain tumor types [adenocarcinoma of lung, melanoma, hematologic malignancies, for example]), have not improved on careful (or expert) light microscopic examination for diagnosis and prognosis. The latter therefore remains the gold standard against which all new technology needs to be assessed. Claims that newer modalities provide greater objectivity should be weighed not only against financial cost and problems of reproducibility in nonspecialized laboratories, but also against the frequency with which such claims seem to be proved wrong. We witness previous descriptions of so-called cancer-specific antigens or mutations, the short-lived misapprehension that

expression of p53 was a reliable marker of the malignant phenotype, or the persistently unproven (and poorly validated) molecular genetic tests, often aggressively marketed, that claim to accurately predict primary site of a cancer or response to chemotherapy. The third (and perhaps more obvious) point is that, as genomic analysis rapidly becomes mainstream, it behooves anatomic pathologists to learn to understand, interpret, and incorporate these data into the daily practice of anatomic pathology. Aside from the fact that this will help to cope with the constantly increasing test volume (by spreading the workload), it will also ensure that pathologists are the ones to integrate histologic and molecular data and therefore provide truly relevant pathology reports.

Once a diagnosis has been reached, then a report must be formulated, guidelines for which are well beyond the remit of a book of this type. However, it is important to ensure that any report provides as much useful information to the clinician as possible; and, in this context, increasingly good reasons exist to use synoptic (or template) reporting formats, especially for common tumor types. In this way, key elements of information are not forgotten and the clinician's ability to interpret a report is maximized. Not only does this mean the inclusion of clear statements regarding tumor type, grade, or stage (where applicable) and status of resection margins, but the report offers a unique opportunity to provide general data concerning clinical features, likely behavior, and ideal management, supported by references to the published literature where appropriate. The transmission of such information may be appropriate only in the case of uncommon or unusual neoplasms, and the extent to which a surgical pathologist will feel able or comfortable to offer advice on therapy will depend greatly on local circumstances and the tolerance or insight of clinical colleagues. In my view, however, surgical pathologists should never forget that they are providing a clinical, often subjective opinion quite different from the type of report required of some other specialties in pathology; and in this circumstance we should not shy away from offering whatever expertise or background data are available to us. It is an extraordinary but undoubted fact that the key articles describing clinical features and therapeutic outcome in many tumor types are published, at least initially, in pathology rather than clinical journals. Often, therefore, surgical pathologists are more likely to have seen and read the latest published studies on the general aspects of a given neoplasm than their clinical colleague. However, any tendency to try and achieve one-upmanship in this relationship should be carefully curbed until such time as pathologists can feel sure that they have also scanned the relevant clinical literature.

To conclude this introductory chapter, I offer some simple truisms applicable to diagnostic tumor pathology that notably have not changed in the past 30 years. Many of these are self-evident and most likely are widely known; the frequency with which they are forgotten is therefore all the more remarkable and regrettable:

1. By virtue of simple statistical probability, common things remain common; therefore do not be tempted into an esoteric (or exciting) diagnosis until you have confidently excluded a more probable diagnosis. A good example that typifies this pitfall is the characterization of spindle-celled malignant neoplasms arising in breast or epithelial-lined viscera, such as the upper aerodigestive tract or urinary bladder; sarcomatoid (or spindle cell) carcinomas are a far more likely prospect than some unusual sarcoma or so-called carcinosarcoma.
2. Pathologists should never be afraid to request a larger (or repeat) biopsy if they are having difficulty in coming to a firm diagnosis before definitive therapy. It is a matter of fact that some tumor biopsies are inadequate or unrepresentative. In fact, the increasing trend for our clinical

and radiologic colleagues to provide smaller and smaller biopsies (in the names of cost effectiveness and convenient patient care) is not only limiting our ability to make definitive diagnoses but also diminishing the opportunity to provide valuable prognostic information. This tide needs to be stemmed, or at least challenged and first validated, especially because the use of preoperative neoadjuvant therapy is also increasing and often renders the ultimate resection specimen relatively useless for diagnostic or prognostic purposes. Painful hours, or even days, of indecision followed by an inconclusive or, worse, inappropriately confident report are far better avoided by a clear request for more tissue. On occasion this undoubtedly prevents the institution of inappropriate therapy. Any attempt to hedge (or spread) one's bets in a diagnostic report should be avoided when possible.

3. Pathologists should never be afraid to admit that they cannot diagnose or classify a given neoplasm. No pathologist on this planet does not sometimes benefit from a second opinion, however intermittent this need may be. Pathologists who believe that they never need a second or specialist opinion are dangerous. Increasingly this becomes true in anatomic pathology, which is ever more subspecialized and in which the days of the true generalist are numbered, if not gone. Conversely, a subset of human tumors will always remain that defy rational classification by anyone. In this context clues may exist (but not always) to the likely clinical behavior of such a neoplasm, even if the line of differentiation is obscure, but such clues should be interpreted only tentatively; the reality is that if one cannot categorize a neoplasm reliably on morphologic grounds, then any attempt at prognostication is inevitably unreliable and only amounts to more or less sophisticated guesswork.
4. The (possibly obvious) corollary of the previous point is that pathologists can diagnose only what they have seen, read, or heard about previously. This sets clear limitations on the interpretative skills of any pathologist and underlines the need to keep abreast of recent continued developments, by either regular attendance at postgraduate meetings or the routine perusal of major journals in our specialty. Those (increasingly few) who insist on regarding the recognition or recategorization of diagnostic entities as worthless splitting do so at their peril; those who attempt to force all tumor diagnoses into categories with which they are already familiar do likewise.
5. A further point that is related, at least peripherally, to the “don't know” situation is that a pathologist (or, for that matter, any practicing physician) should never be afraid to admit a mistake. Every pathologist has made at least an occasional error, however trivial or clinically insignificant, and anyone who suggests otherwise is probably deluded. Our specialty is an interpretative skill or art, not a black-or-white measurement, and therefore human error is unfortunately inevitable. Far more trouble can be generated by concealment or dishonesty in this regard than by admitting a suboptimal diagnosis.
6. Prognostication in cancer management, especially among clinical oncologists, is often believed to rely largely on tumor grade and stage, both of which the pathologist may be instrumental in assessing. Some clinicians believe that such parameters (particularly grade) can be determined in the absence of a specific diagnosis. In the light of the foregoing discussion, this is clearly most often nonsensical, and it is up to surgical pathologists to resist such demands when appropriate. In many organ systems, the principal determinant of likely outcome is accurate histologic typing,

and the importance of an unequivocal diagnosis should never be underestimated. Equally in some types of cancer, substratification by grade is meaningless, because a given tumor type may invariably be biologically low grade (e.g., infantile fibrosarcoma) or high grade (e.g., pleural malignant mesothelioma), irrespective of histologic appearances. Therefore it is important to recognize that grading (and often also staging) systems need to be tailored, in many cases, to the individual tumor type, and this is one circumstance in which generalizations can undoubtedly be dangerous. In parallel, we need to take care that the rush to incorporate mutational analysis as a component of prognosis or treatment selection (as, for example, in gastrointestinal stromal tumors and non–small cell lung carcinomas) does not bypass careful validation studies, remains confined to the tumor types for which such validation has been achieved, and has demonstrable clinical impact. For the relative lack of significant therapeutic advances in some tumor types to hide behind the use of ever more sophisticated (and expensive) diagnostic or prognostic technologies is not a desirable outcome.

This discussion also begs the question of what constitutes a high-grade neoplasm; there are no easy answers to this question, but the following examples provide food for thought and should prompt careful appraisal of the manner in which we, as doctors, assess malignant neoplasms. Consider the following three patients: The first is a 60-year-old man with an inoperable small cell carcinoma of bronchus; we know that his tumor is likely to disseminate rapidly, despite chemotherapy, and his prospects of surviving more than 12 months are slim. The second is a 25-year-old woman with localized alveolar soft-part sarcoma of the thigh; we know that her 5-year survival probability is 60% to 70%, and, with this information, she may well form a stable relationship and start a family—but we also know that her chances of surviving beyond the age of 45 years are no more than 15%, because most patients with this type of tumor eventually develop distant metastases. The third is a 45-year-old with a grade 2 astrocytoma in the frontal lobe; we know that the risk of extracranial spread (metastasis) is very small but that the chances of postsurgical recurrence are high; we also know that such recurrences are likely to be progressively fatal over a 5- to 10-year period. I believe that all three patients would be justified in claiming that they had a biologically high-grade neoplasm, yet the perception of the physician, pathologist, or scientist in each case would undoubtedly be different, particularly with regard to the inherent biology of these tumors. This variability underlines the need to treat tumors on the basis of biologic rather than histologic grade, at least in those circumstances in which our therapeutic options allow any flexibility.

7. The last and perhaps most straightforward truism is that histology reports, whether on specimens from one's own hospital or from a patient thousands of miles away, should be as prompt as is feasible and safe. The surgical pathology report is not simply a matter of record or a means of rubber-stamping a clinical suspicion; in the context of tumor pathology, almost always it is the diagnostic arbiter and a major determinant of therapy. It impinges enormously on patients, even if they are commonly unaware of this fact. Any pathologist who fails to recognize or shoulder this responsibility might best be advised to consider alternative employment.

CHAPTER 2

Tumors of the Heart and Pericardium

Henry D. Tazelaar, Joseph J. Maleszewski

CHAPTER OUTLINE

Tumors of the heart and pericardium are, as in most sites, broadly dichotomized into benign and malignant varieties. Among the benign tumors, some are correctly classified as neoplasms, some as nonneoplastic entities, some as hamartomas or heterotopias, and some as processes somewhere in between. No firm distinctions pertaining to histogenesis are drawn in this discussion as the emphasis is on accurate diagnosis. It is important to note that, although the tumors discussed in this chapter represent primary cardiac tumors, by far the most commonly encountered cardiac tumors are metastatic lesions from other primary sites (most commonly lung, breast, and cutaneous melanoma).

More than 90% of primary cardiac tumors are benign, with the majority in adults being myxomas. In infants and children the most common primary tumor of the heart is the rhabdomyoma. Malignant cardiac and pericardial tumors, like malignant tumors elsewhere in the body, have the ability to invade and metastasize. Benign cardiac tumors as well, however, can have clinically malignant consequences given the frequency of endocardial or conduction system involvement. Box 2.1 lists the most common cardiac tumors, including true neoplasms, hamartomas, and nonneoplastic entities.

Box 2.1

Major Primary Tumors (Neoplasms, Hamartomas, and Pseudotumors) of the Heart and Pericardium

BENIGN	MALIGNANT
Myxoma	Angiosarcoma
Rhabdomyoma Fibroma Lipoma and lipomatous hypertrophy of atrial septum Papillary fibroelastoma Histiocytoid cardiomyopathy Teratoma Hemangioma Cystic tumor of the atrioventricular node Hamartoma of adult cardiac myocytes Paraganglioma Calcified amorphous tumor (CAT) Mesothelial/monocytic incidental cardiac excrescences (MICE)	Undifferentiated high-grade pleomorphic sarcoma Rhabdomyosarcoma Leiomyosarcoma Malignant mesothelioma Lymphoma

General Clinical Features

The clinical manifestations of cardiac tumors are often nonspecific. Indeed, many other diseases may be mimicked. The clinical presentation is usually subdivided under three major headings: (1) systemic, (2) embolic, and (3) cardiac. Clinical features reported to occur with each tumor will not be mentioned in the discussion of that tumor, unless specific to that tumor for some reason.

Systemic Manifestations

The systemic manifestations of tumors of the heart are manifold and include findings such as fever, cachexia, and malaise. Abnormal laboratory findings that may develop include an elevated erythrocyte sedimentation rate, hypergammaglobulinemia, thrombocytosis or thrombocytopenia, polycythemia, leukocytosis, and/or anemia. The mechanisms that underlie these systemic manifestations are not as yet fully understood, but it is likely that they relate to cytokine elaboration.[1–3]

Many cardiac tumors are also associated with clinical systemic syndromes and genetic diseases. A summary is found in Table 2.1.

TABLE 2.1

Genetic Syndromes Associated With Cardiac Tumors.

Tumor Type	Associated Syndrome	Involved Gene(s)	Chromosome Location	Inheritance Pattern	Syndrome Prevalence	Association with Syndrome (%)
Myxoma[1,2]	Myxoma syndrome	*PRKAR1A*	17q2	AD	Rare (~500 cases worldwide)	~7
Rhabdomyoma[3]	Tuberous sclerosis	*TSC1/TSC2*	9q34/16p13	AD (1/3), sporadic (2/3)	1 in 6000 (at birth)	~90
Fibroma[5,6]	Nevoid basal cell carcinoma syndrome (Gorlin syndrome)	*PTCH1*	9q22.3	AD (1/3), sporadic (2/3)	1 in 57,000	~4
Paraganglioma[7,8]	VHL Neurofibromatosis type 1, MEN-2A, -2B FPPS	*VHL*	3p25 (*VHL*)	AD and AD with maternal imprinting (*SDHD*)	1 in 36,000 (VHL) 1 in 35,000 (MEN-2) 1 in 1,000,000 (FPPS)	~5
		NF1	17q11 (*NF1*)			
		RET	10q11 (*RET*)			
		SDHB	1p36 *SDHB*			
		SDHC	1q21 *SDHC*			
		SDHD	11q23 *SDHD*			
Histiocytoid cardiomyopathy[9–11]	H1CMP	*NDUFB11* Mitochondrial genes	X chromosome, mitochondrial DNA	AR, X-linked and maternal	Rare	~100
Angiosarcoma[264]	Li-Fraumeni–like syndrome	*POT1*	7q31.33	AD	Rare	Unknown

AD, Autosomal dominant; *AR,* autosomal recessive; *FPPS,* familial pheochromocytoma-paraganglioma syndrome; *MEN,* multiple endocrine neoplasia; *VHL,* von Hippel–Lindau syndrome.

Modified from Jain D, Maleszewski JJ, Halushka MK. Benign cardiac tumors and tumorlike conditions. *Ann Diagn Pathol* 2010;14:215–230.

Embolic Manifestations

These events can be due to embolization either of the tumor itself or of thrombi on the surface of the tumor. Embolization of tumor fragments can occur only when the tumor itself shows intracavitary extension. Thromboemboli, on the other hand, can also occur with intramural tumors, which compromise the function of the heart leading to intracavitary thrombosis.

The pathologist may be the first to suspect the presence of a cardiac tumor on the basis of examination of a peripheral embolus. In fact, sudden occlusion of a peripheral artery in an otherwise healthy person should always raise the possibility of a cardiac tumor. An embolectomy specimen therefore should be examined most carefully for the presence of tumor fragments. However, even when only recent thrombotic material is found, it is wise to mention the possibility of a coexistent cardiac tumor. Moreover, multiple systemic emboli may mimic systemic vasculitis or infective endocarditis, particularly when associated with systemic manifestations. Primary tumors of

the right heart chambers may cause pulmonary emboli, which may be indistinguishable from those occurring as a result of venous thromboembolism.

Cardiac Manifestations

The cardiac events that can develop as a result of cardiac tumors are largely determined by the location and size of the tumor. Tumors that are localized in the myocardium usually lead to impaired myocardial function either through substantial replacement of the myocardium by tumor or because of extension into a cardiac chamber. Intramural location may lead to a wide variety of rhythm disturbances, including atrial and ventricular fibrillation. Sudden death may thus be the first manifestation of a cardiac tumor. Primary tumors with intracavitary extension may also cause obstruction and interfere with valve function.

Pericardial effusion, sometimes with signs and symptoms of cardiac tamponade, is usually a result of either epicardial extension or a primary pericardial tumor.

Benign Tumors of the Heart and Pericardium

Myxoma

Clinical Aspects

This is frequently cited as the most common primary heart tumor, although nonneoplastic entities (e.g., thrombi) and the papillary fibroelastoma (of uncertain histogenesis) are actually more common.[4] Nevertheless, it is likely that they represent the most common primary cardiac neoplasm. It is a tumor of adults, occurring most often in women aged 20 to 60 years. Most occur sporadically, but about 7% are associated with the Carney complex (CNC). This autosomal dominant syndrome characterized by the presence of multiple myxomas, spotty pigmentation, and endocrine overactivity (Table 2.2) has been given a variety of eponyms and acronyms[5–7]: Swiss syndrome, NAME syndrome (nevi, atrial myxoma, myxoid neurofibroma and neurofibromata, and ephelides), LAMB syndrome (lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi), and myxoma syndrome. In patients with CNC, the myxomas tend to occur in locations other than the left atrium, may be multiple, and have a much higher recurrence rate compared with that in patients who have nonsyndromic myxomas (21% vs. 1%–2%).[7] Moreover, recurrences tend to show more rapid growth[8] and more pronounced local invasiveness.[9] A complete list of the features that differentiate nonsyndromic myxomas from those that arise in the setting of CNC can be found in Table 2.3. Cutaneous myxomas should not be mistaken for metastatic cardiac myxomas in this population.[10,12-15]

TABLE 2.2

Clinicopathologic Features of the Carney Complex.[a]

Feature	Comments
Male sex: 67%	Compared with 24% for nonfamilial cases
Mean age at presentation: 24 yr	Compared with 51 yr for nonfamilial cases
Myxomas	
Cardiac	Unusual locations, multiple, recurrent
Skin	Multiple
Breast	Myxoid fibroadenomas
Spotty mucocutaneous pigmentation	Scleral and vermillion borders of lips: lentigines, blue nevi, and combinations
Psammomatous melanotic schwannomas	
Primary pigmented nodular adrenocortical disease	Cushing syndrome
Testicular tumors	Characteristically Sertoli cell tumors, usually bilateral and multicentric
Pituitary growth hormone–secreting adenomas	Acromegaly or gigantism

[a]Not all features occur in any one patient.

TABLE 2.3

Differences Between Nonsyndromic and Syndromic Myxomas.

Features[16]	Nonsyndromic	Syndromic
Average age (yr)	51	24
Age range (yr)	17–75	4–48
Sex ratio (male:female)	1 : 3	2 : 1
By location[a]	86% in left atrium 18% in right atrium	62% in left atrium 37% in right atrium 21% in right ventricle 4% in left ventricle
Multicentric (%)	6	33
Recurrence rate (%)	3	20

[a]Some patients have myxomas in more than one anatomic location.

Gross Pathology

The vast majority of cases (approximately ≥90%) arise in the atria, with a significant predilection for the septum of the left atrium. Tumors may less commonly arise in the right atrium and much less often, the ventricles.[16–22] Tumors arising in a location other than the classic left atrium increase the likelihood that the patient has CNC. Although historic debate about this has occurred, myxomas may also originate from any cardiac valve.[16,21,23–26] It is of additional interest that, among the reported valvular cases of such myxomas, a right-sided heart location appears

to be more common than a left-sided one and that the tumors may be attached to either the inflow or the outflow surface of the valve.

Cardiac myxomas are either pedunculated or sessile. They may be globular, almost round masses with a smooth surface (Fig. 2.1) or villiform with multiple thick papillary fronds (Fig. 2.2). They range from pale gray to dark red, and variegation within a single tumor is common. Occasionally surface thrombus may be present, particularly on villiform tumors. Myxomas are usually soft and friable with a distinctive gelatinous appearance and consistency (Fig. 2.3). Somewhat expectedly, it is the villiform variety that tend to be more friable and have the highest propensity to embolize and be identified in downstream vessels (Fig. 2.4). Some myxomas may be firm, and occasionally gross calcifications may be observed, even to the extent that the bulk of the tumor consists of a calcified mass. This condition is known also as *petrified cardiac myxoma* (Figs. 2.5 and 2.6) and may be mistaken for an atrial thrombus clinically.[27] Multiple tumors are most often associated with CNC (Fig. 2.7).

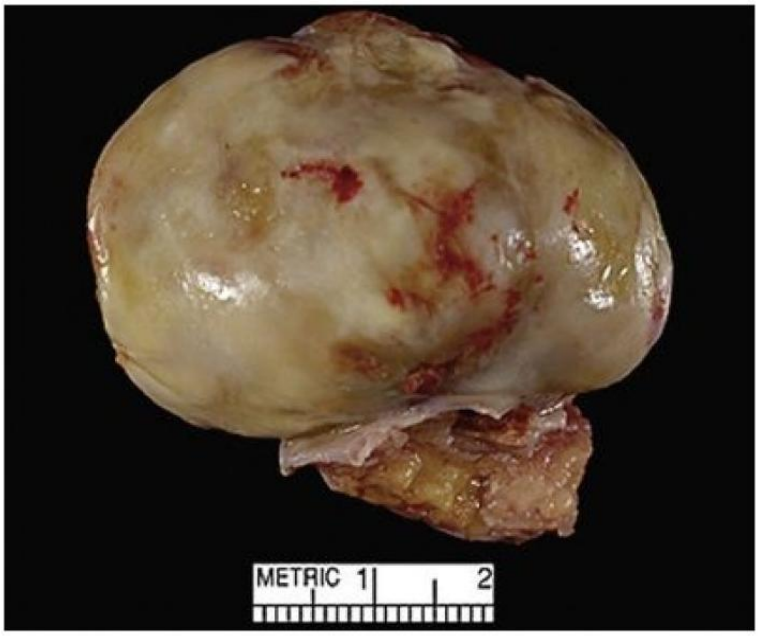

FIG. 2.1 Myxoma with stalk and smooth globular shape. (Courtesy Dr. William D. Edwards, Mayo Clinic, Rochester, MN.)

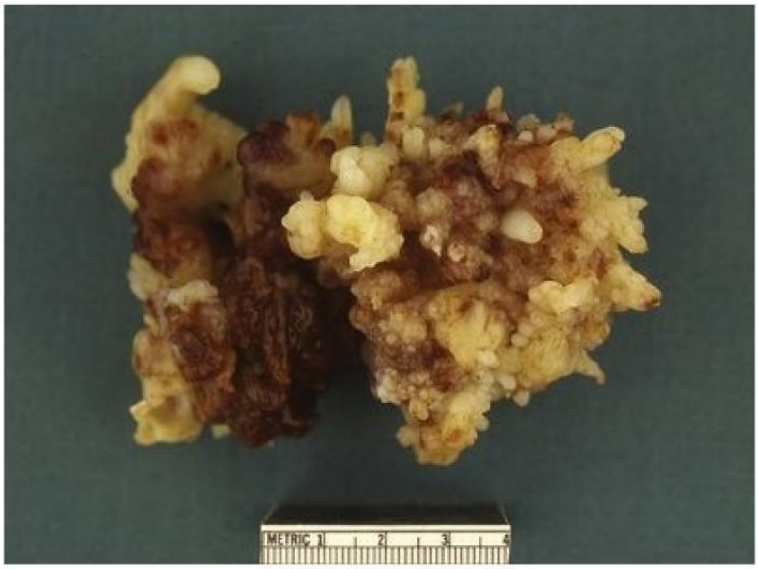

FIG. 2.2 Myxoma with papillae. Note that the papillae are broad and thick. (Courtesy Dr. Caterina Giannini, Mayo Clinic, Rochester, MN.)

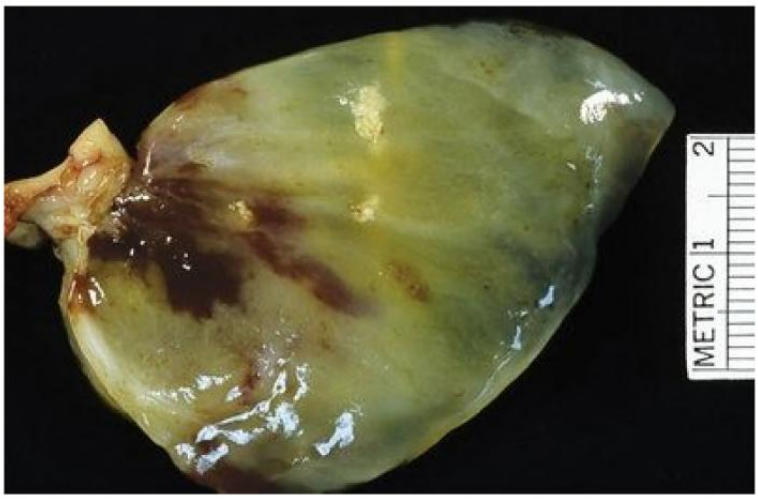

FIG. 2.3 Myxoma with glistening surface and gelatinous consistency.

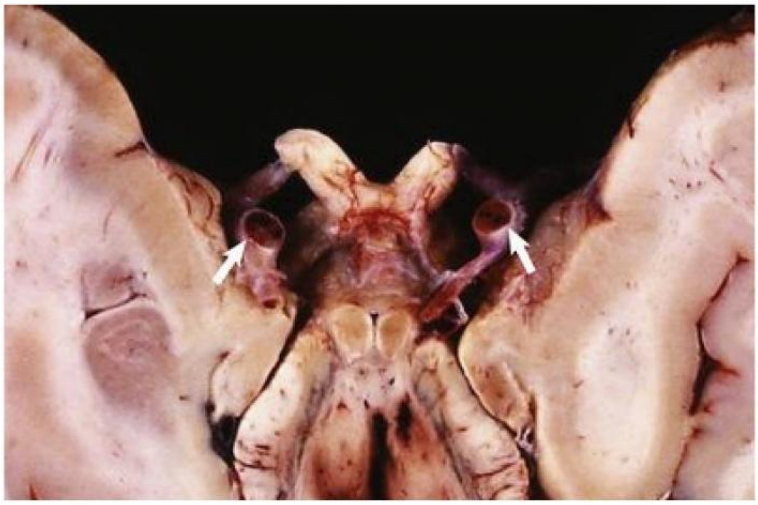

FIG. 2.4 The undersurface of the brain shows bilateral internal carotid artery obstruction *(arrows)* by myxoma emboli. (Courtesy Dr. Joseph E. Parisi, Mayo Clinic, Rochester, MN.)

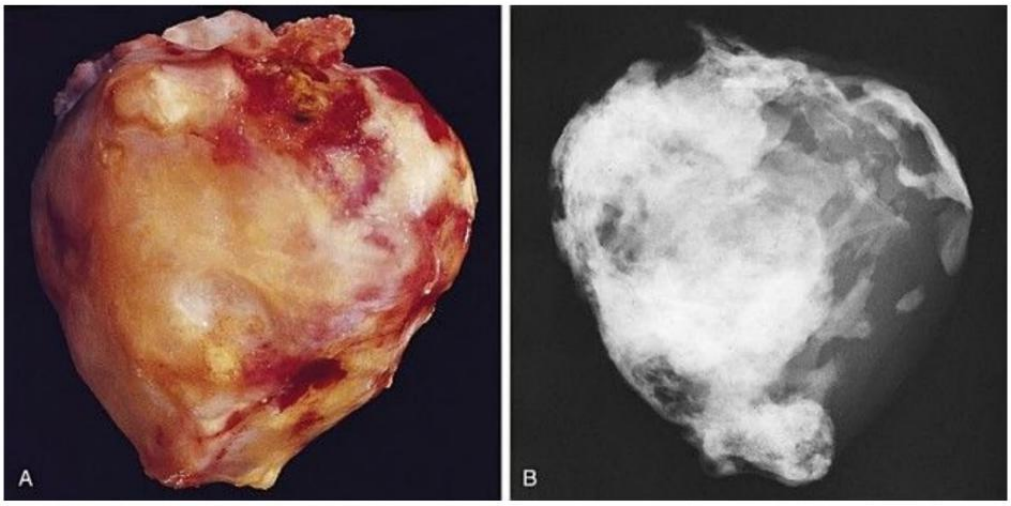

FIG. 2.5 Markedly calcified myxoma, so-called petrified myxoma from the left atrium of a 48-year-old man (A) and its specimen radiograph highlighting heavy calcifications (B).

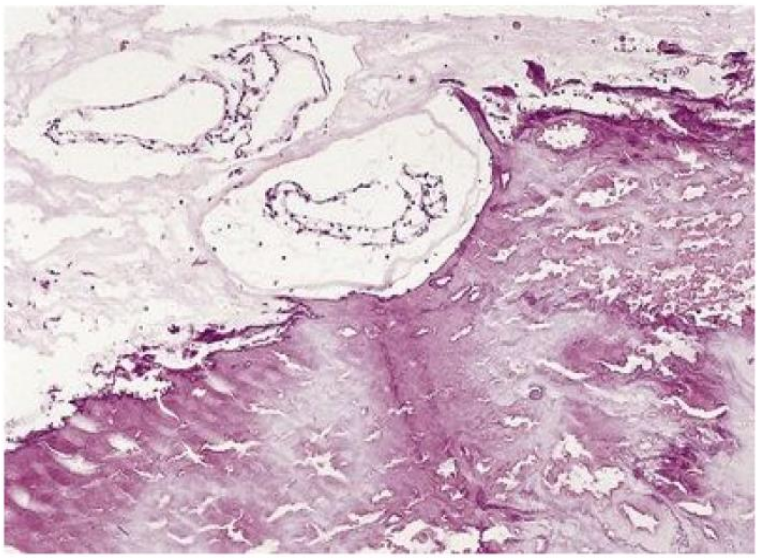

FIG. 2.6 Markedly calcified myxoma. Histology of specimen depicted in Fig. 2.5 shows foci of calcification adjacent to nests of myxoma cells revealing the myxomatous nature of this lesion.