Renal Pathology Series: Kidney Transplant

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Renal Transplant Pathology Series-V: Category 4

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Banff classification of renal allograft pathology has evolved considerably over the past 30 years and has undergone significant changes in many of the original diagnostic categories. With this evolution, it has increased in complexity and level of difficulty. To make it user friendly, this series of tutorials has been planned. In this pictorial, we aim to provide an illustrated presentation of the Banff classification categories and practical tips and tricks to identify and report the lesions. This will be useful for better understanding of renal transplant pathology for trainees and residents of nephrology and histopathology as well as for practicing pathologists and nephrologists.

Banff category 4. Acute rejection (Acute/active T-cell-mediated rejection [TCMR])

The spectrum of TCMR is defined as Banff diagnostic category 4 which contains acute TCMR Grade IA, IB, IIA, IIB, III as well as chronic active TCMR Grade IA, IB and II. In the previous issue of this journal, borderline changes (category 3) was discussed. Banff diagnostic categories 3 and 4 are mutually exclusive but can be diagnosed together with other lesions from categories 2, 5 and 6.

As discussed in previous issues of this tutorial, in earlier versions of the Banff schema the main focus was on the diagnosis and categorization of acute/active cell-mediated rejection. In fact, this focus on cellular rejection overshadowed the characterization and recognition of antibody-mediated rejection (ABMR) for quite some time in the earlier days of Banff era. However, more recently, with an increasing recognition and reporting of ABMR, major and drastic changes have been effected in the diagnostic criteria and classification of this category. On the other hand, the category of cell-mediated rejection has lagged behind in this context. In fact, the most important changes in this category took place during the early Banff meetings (Tables 1, 2). More recent Banff updates have made only minor changes in the nomenclature, morphological criteria and subcategorization of this entity (Table 3).

Table I. The grading of acute/active rejection in Banff 93 working classification.

Category 4.	Acute rejection
Grade I: Mild acute rejection (AR)	Cases fulfilling the criteria of significant interstitial lymphocytic infiltration, i2 (> 25% of parenchyma affected) and foci of moderate tubulitis, t2 (> 4 mononuclear cells/tubular cross section or group of 10 tubular cells).
Grade II: Moderate AR	Cases with (A) i2 and foci of severe tubulitis, t3 (>10 mononuclear cells/tubular cross section) and/or (B) mild or moderate intimal arteritis, v1 or v2.
*Grade III: Severe AR**	Cases with severe intimal arteritis and/or "transmural" arteritis with fibrinoid necrosis of medial smooth muscle cells, v3.

*Recent focal infarction and interstitial hemorrhage without other obvious cause were also considered compatible with Grade III rejection.

As noted above the main focus of the first Banff classification was on the diagnosis and classification of acute rejection, which practically includied acute/active cell-mediated rejection. This type of rejection is characterized by accumulation of mononuclear cells, mostly T lymphocytes and macrophages, first in the interstitium, followed by infiltration of these cells into tubules or arteries, resulting in tubulitis or arteritis. Thus, the principal targets of cellular rejection are different from those of ABMR. Prior to Banff classification, the presence of merely a few lymphocytes anywhere in the biopsy was often considered as a harbinger of rejection. However, Banff made several important and novel contributions to the diagnosis and standardization of morphological criteria of rejection diagnosis. It introduced for the first time a minimum threshold for a definitive diagnosis of acute/active cell-mediated rejection. A corollary of this was the creation of a category of borderline changes in cell-mediated pathological processes, which was discussed in the previous issue of this journal. It also recognized the importance of the location of the inflammatory cell infiltrate in the biopsy during earlier iterations of the classification.

Table 2. Banff 97 typing of acute/active rejection.

Category 4.	Acute/active rejection
Type I: Tubulointerstitial type	
Type IA:	Significant interstitial inflammation, i2 (>25% of non-scarred cortex)+ moderate tubulitis, t2 (> 4 lymphocytes/tubular cross section)
Type IB:	Significant interstitial inflammation, i2 (>25% of non-scarred cortex)+ severe tubulitis, t3 (> 10 lymphocytes/tubular cross section)
Type II: Vascular type, Intimal arteritis	
Type IIA:	with < 25% luminal occlusion (v1)
Type IIB:	with >25% luminal occlusion (v2)
Type III: Severe type	
Transmural arteritis or fibrinoid necrosis (v3)	

It should be noted, as will become evident later on, that the above criteria and thresholds, are required for the diagnosis of tubulointerstitial or type I rejection. Here, the rationale for creating the borderline category was that the morphological lesions of rejection build up gradually; hence, if biopsies are done too early, pathologists often feel difficulty in definitively diagnosing rejection, owing to the inflammatory and tubulitis scores not reaching the threshold for rejection diagnosis. There is no borderline category for vascular or type II rejection and presence of even one lymphocyte in the intima is sufficient to diagnose a case as vascular rejection. The nomenclature of this category has changed from acute rejection to acute cellular rejection to TCMR over the years, as shown in Table 3.

Table 3. The main evolutionary changes in the diagnostic category of T-cell-mediated rejection in Banff classification.

Pre-Banff	1st Banff	Banff '97	Banff '97 Update	Banff '05	Banff '07
Acute rejection	Acute rejection	Acute/active rejection	Acute/active cellular rejection	T-cell-mediated rejection (TCMR)	T-cell-mediated rejection (TCMR)
	Grades I, II, III	Type I A, B	Type I A, B	Acute TCMR	Acute TCMR
		Type II A, B Type III	Type II A, B Type III	Type I A, B	Type I A, B
				Type II A, B Type III	Type II A, B Type III
				Chronic active TCMR	Chronic active TCMR

Note: The changes in the nomenclature and classification are highlighted by underlining the additions.

Regarding the classification of TCMR, the first Banff classification categorized acute/active rejection into three "grades" of increasing severity, as shown in Table 1. This classification lumped together both the tubulointerstitial and vascular rejections. The grades were: grade I or mild, grade II or moderate and grade III or severe (shown in Table 1). Little consideration was given to the underlying pathogenetic basis of rejection in this categorization. The first major change in this category took place in Banff 97 meeting, when pathologists using the Banff 93 classification and CCTT classification got together and adapted the Banff 97 classification with significant contributions from the CCTT classification, which emphasized the pathogenetic basis for the classification of cellular rejection. Banff 97 classification categorized acute/active rejection into "types" and subtypes instead of grades (Table 2). The major changes in Banff 97 included the separation of type I or tubulointerstitial rejection from vascular or type II rejection. Type III rejection was categorized separately as in Banff 93 classification (Table 2). This change signified the flexibility of the Banff group to accommodate the views of investigators using CCTT classification and also assimilate the experience from newer studies showing that vasculitis per se has siginificant implications for response to therapy and/or graft survival.

In Banff 97-update published in 2003, with significant changes in the category of ABMR, the category of acute/active rejection was renamed as acute/active cellular rejection, to emphasize its distinction from ABMR. The typing and subtyping, however, remained the same as in Banff 97 classification (Table 2). The name of the category was again changed to TCMR in Banff 2005 update (Table 3). This time, it was further divided into acute TCMR, which now included all the subtypes of acute/active cellular rejection of Banff 97-update, and the chronic active TCMR. The later was defined by the presence of chronic allograft arteriopathy only characterized as arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima. Banff 2007 classification added a new lesion score, termed ti (total interstitial inflammation score) to the schema. Not much was changed in the criteria for diagnosis or classification of cellular rejection during Banff' 09, Banff 2011 and Banff 2013 meetings. In Banff meeting of 2015, it was realized and acknowledged that chronic active TCMR may express itself in tubulointertitial compartment in the form of i-IFFA (inflammation in areas of scarring) in addition to arterial lesions.

It is apparent from the above discussion and the illustrations that follow that the mainstay for the diagnosis and classification of cellular rejection has been the morphology with little help from ancillary techniques of immunohistochemistry (IHC) or electron microscopy (EM). More recently, attention has been focused towards the use of molecular markers of acute cellular rejection with promising results in single center studies. Multicenter trials and standardization of the methodology represent future challenges for the Banff group. The molecular data may be combined with the morphological data in the Banff classification in near future to increase the accuracy of diagnosis and classification of rejection, particularly borderline and chronic active TCMR cases.

In conclusion, the development of the Banff classification of the renal allograft pathology has steamlined standardization of approaches to rejection diagnosis and classification and reduced interobserver and interinstitutional variations. The mainstay of diagnosis and classification of cellular rejection is still morphology. Molecular profiles may help fine tune the diagnosis and classification criteria in near future.

A series of representative images of biopsies with category 4 (TCMR) of Banff classification are illustrated in Figures 1 to 8.

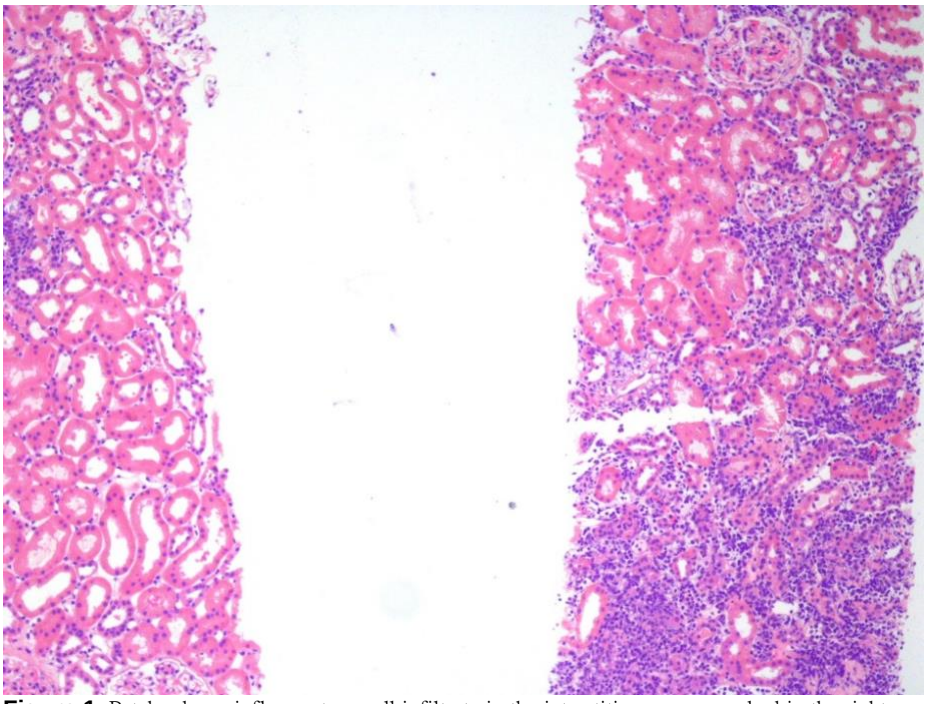

Figure 1. Patchy dense inflammatory cell infiltrate in the interstitium, more marked in the right core. It is difficult to discern the nature of cellular infiltrate at this magnification. Such cellular infiltrates may be seen in rejection, infection, tubulointerstitial nephritis, and posttranspaont lmyphoproliferative disorders (H&E, ×100).

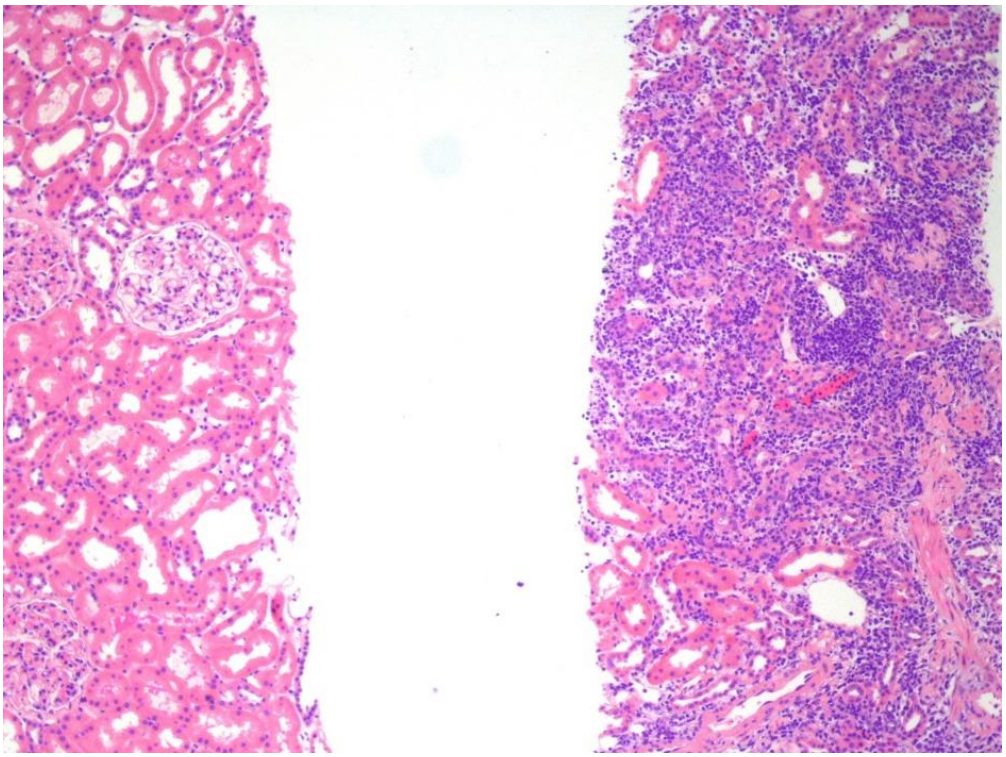

Figure 2. Patchy dense inflammatory cell infiltrate in the interstitium in one of two cores (right). This patchy distribution of infiltrates is common, especially during early phase of rejection and can result in underdiagnosis of rejection. Hence, the emphasis on sample size in the Banff classification. It is difficult to discern the nature of cellular infiltrate at this magnification. (H&E, ×100).

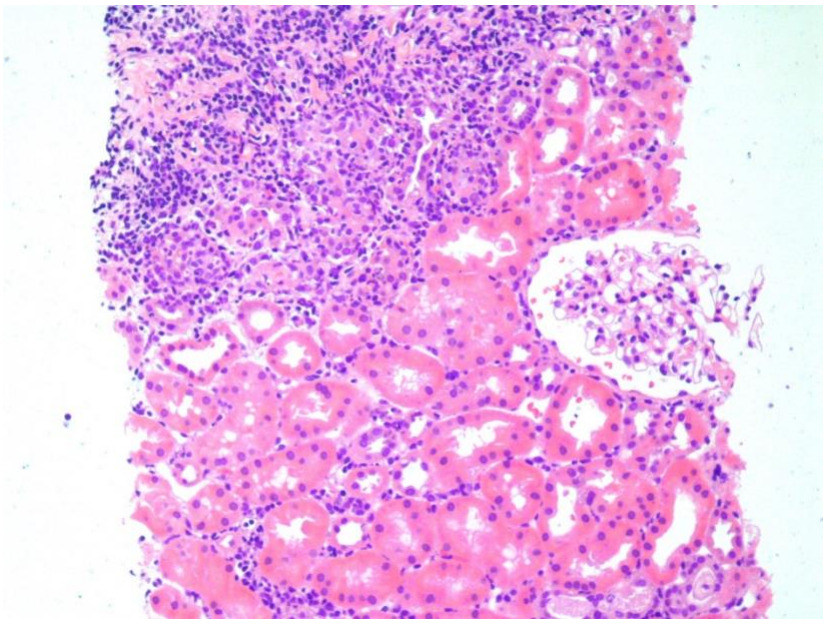

Figure 3. Patchy dense inflammatory cell infiltrate in the interstitium involving upper third to half of the core. Majority of cells appear to be mononuclear at this magnification. This type of inflammatory infiltrate is the hallmark feature of rejection and is designated as i in scoring system of Banff lesion scoring, but is not sufficient on its own to diagnose tubulointerstitial or type I rejection without concurrent tubulitis (t2 or t3) or arteritis (any v). One glomerulus included shows no glomerulitis or double contouring (H&E, ×200).

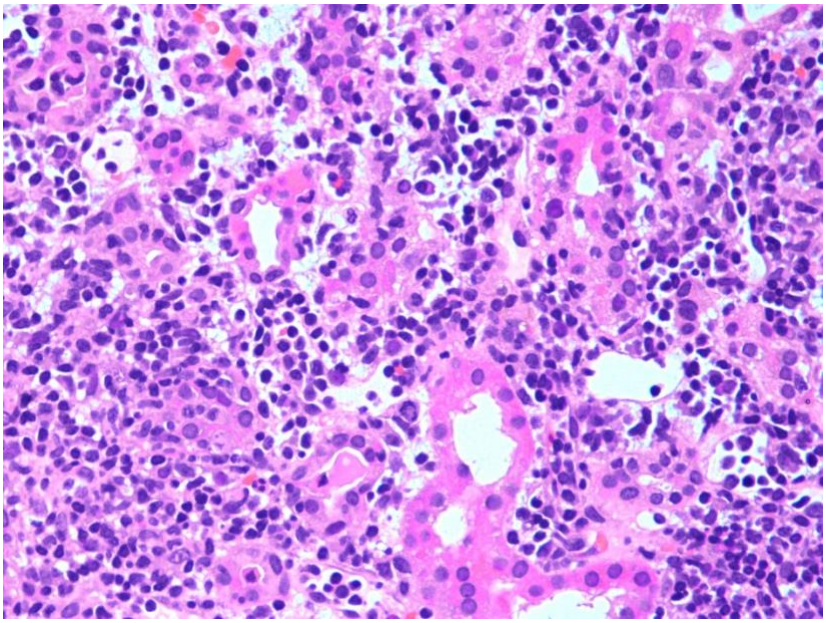

Figure 4. Almost diffuse dense inflammatory cell infiltrate in the interstitium involving the entire visible area of the core associated with mild interstitial edema. Majority of cells appear to be mononuclear (lymphocytes and macrophages) at this magnification. An occasional plasma cell and eosinophil are also evident. For detection of tubulitis, PAS or silver stains are useful (H&E, ×400).

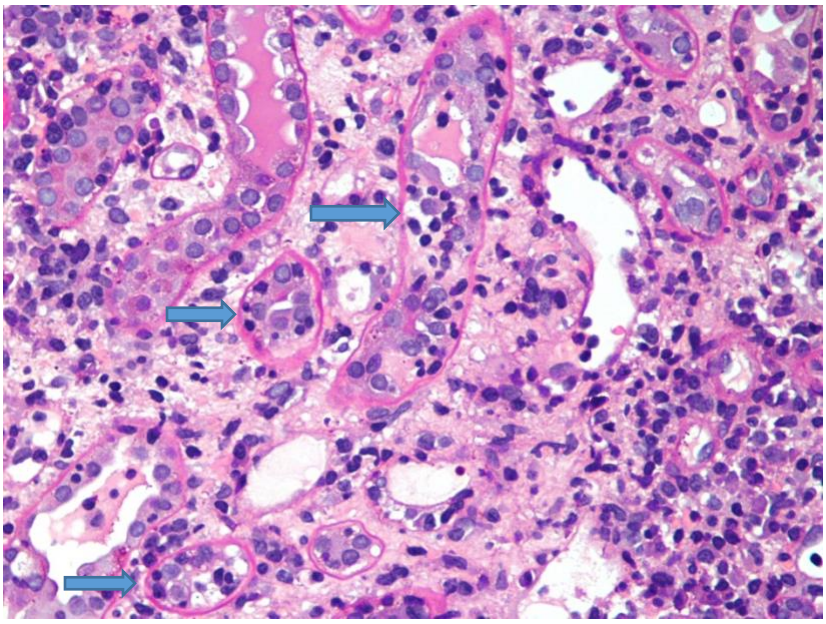

Figure 5. Many tubules in this representative area of biopsy show significant tubulitis of t2 (5 to 10 cells per tubular cross section) and t3 (more than 10 cells per tubular cross section). Presence of this degree of tubulitis along with i2 is sufficient to diagnose a case of acute TCMR (PAS, ×400).

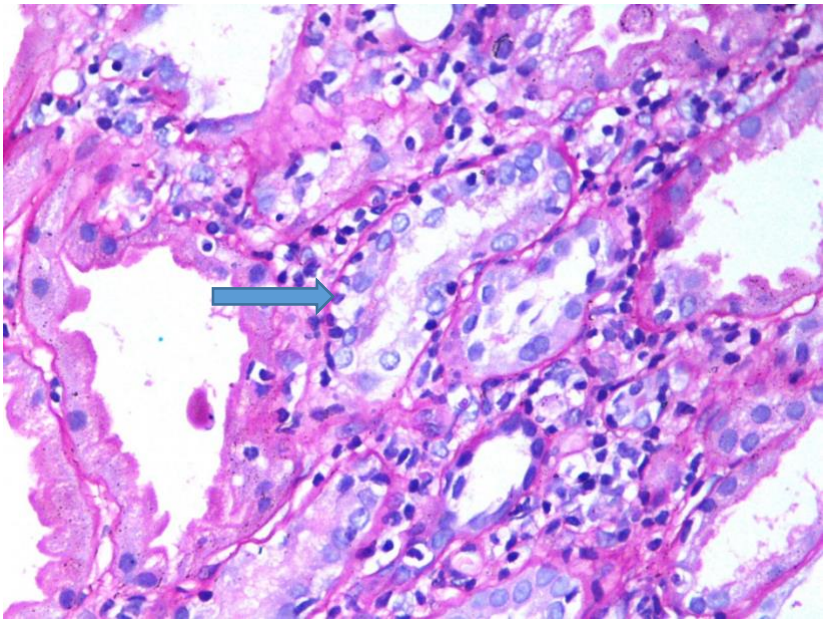

Figure 6. Presence of even one non-atrophic tubule with significant tubulitis of t2 (5 to 10 cells per tubular cross section) or t3 (more than 10 cells per tubular cross section) in the backdrop of interstitial inflammation of i2 or i3. Presence of this degree of tubulitis along with i2 is sufficient to diagnose a case of acute TCMR (PAS, ×400).

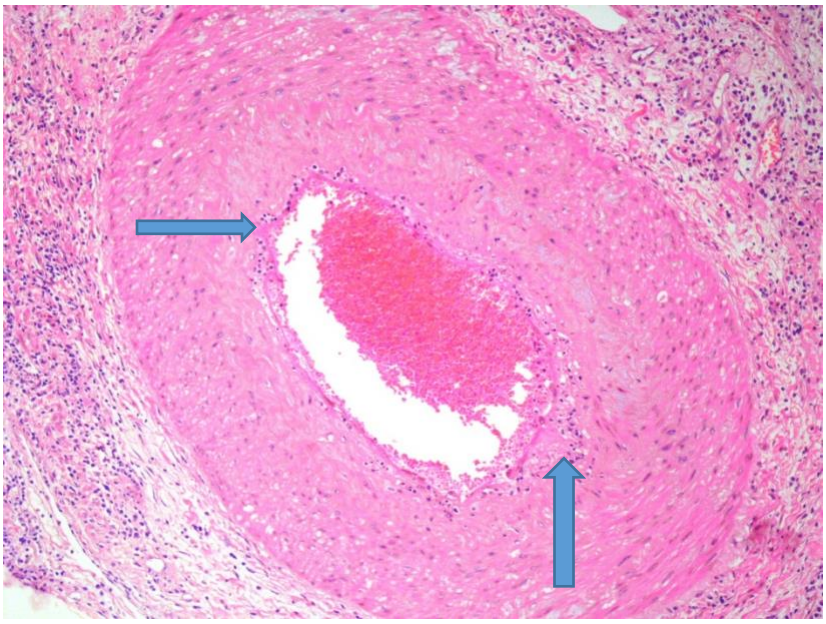

Figure 7. Presence of scattered lymphocytes in the intima of an artery is diagnostic of acute vascular rejection. Presence of a single lymphocyte in the intima is sufficient to diagnose a case of acute vascular rejection. This degree of intimal arteritis qualifies for v1 score according to Banff criteria (HE, ×200).

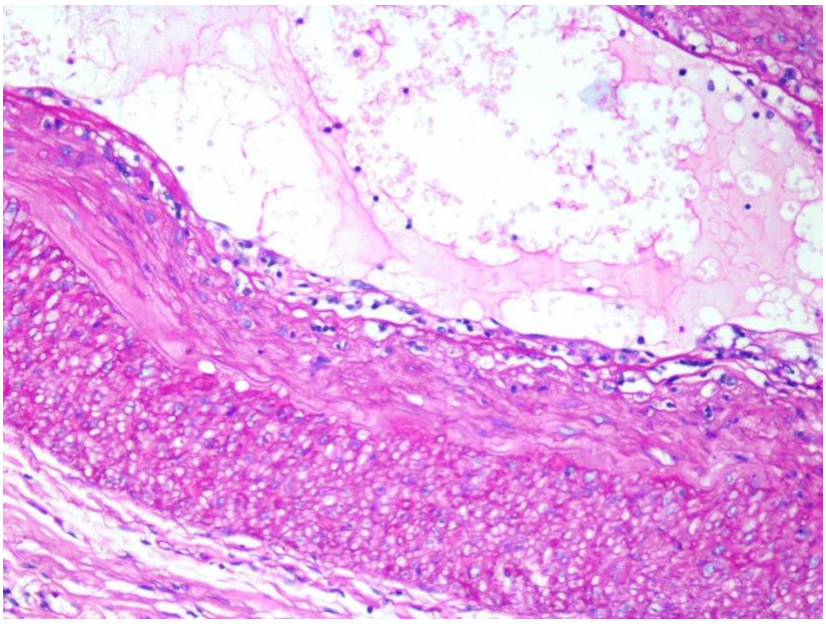

Figure 8. Presence of scattered lymphocytes in the thickened intima of an artery is diagnostic of chronic active TCMR. However, similar changes may be observed in chronic active ABMR (PAS, ×400).

Further reading:

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