**Discussion**

Tuberculosis is a global health problem and a very common cause of morbidity and mortality in children especially in the developing world. It is caused by Mycobacterium tuberculosis (MTB). It can affect both children and adults and is commonly a result of person-to-person transmission. Primary infection usually occurs in childhood due to exposure to other infected family members. In most instances the primary involvement is usually the lungs.

The apices of the lungs are the preferred sites where bacilli result in host cell-mediated response that brings macrophages to the site. The bacilli are ingested by the macrophages and the resulting inflammatory response and cytokine release of TGF-β, Interferon-γ result in release of nitric oxide radicals and destruction of the bacteria with associated caseation necrosis, giving rise to the classic granulomas. The infection subsequently drains into the hilar lymph nodes thus giving rise to the Ghon complex. The lesion may then calcify and may persist as a latent infection for years. This is true of more than 70% of cases of tuberculosis. Active infection can result at any age and may be a result of reactivation of the latent bacillus or reinfection, which is thought to be the more common event. This course may be altered in immunocompromised patients and in young children in whom the cell mediated immune response is incapable of destroying the bacillus resulting in progression of the infection causing extrapulmonary manifestations including skeletal, cerebral and miliary tuberculosis.

Miliary tuberculosis appears to affect very young children (1-5 years of age) more commonly than older children. It is often associated with a negative skin test in almost 50% of the cases. It occurs usually with 3-6 months of primary infection in children. It can involve multiple organ systems and results in studding of organs by minute 1-2 mm tan yellow nodules resembling millet seeds, giving them the name of miliary TB. Histologically, they are associated with minute foci of coalescing or distinct granulomas with caseation. The mortality rate in disseminated miliary TB is about 7-12% in children. The gold standard for diagnosis remains identification of acid fast bacilli in sputum or bronchoalveolar
lavage specimens, although this can be challenging in the very young. The PPD test is unreliable in this disease and is also associated with a high proportion of false positive and negative results and hence new ELISA tests on whole blood and an EliSPOT test are also available. These are helpful in that they are based on the release of interferon-γ in response to infection and hence help differentiate in many cases latent TB from active infection. The ELISA based methods also have the advantage of not being affected by the BCG immunization status of the patient. Although PCR is an extremely sensitive method to detect small numbers of organisms, it may not help differentiate between latent and active infection. Tissue PCR can however be used in acid fast negative cases for diagnostic confirmation. Microbiologic cultures on liquid media are usually confirmatory and also help in determining the drug sensitivity of the organism. Cultures however take at least 21 days for the organisms to grow.

The cellular basis of MTB infection and tissue persistence is now better elucidated. Once phagocytosed by the macrophages, they reside in the phagosome that does not progress to an endosome. This releases cytokines and the resulting cellular infiltrate including the strong cell-mediated (Th1) response results in granuloma formation and control of the infection including killing of the bacteria. TNF-α is especially important in granuloma formation. The resulting destruction leads to the caseous necrosis. Some bacteria however survive this process through unknown mechanisms and remain in the state of latency. Reactivation or progression to active disease is the result of cell-mediated immunity. A complex response of cytokines develops involving interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-2 and interleukin-12. Over the ensuing 4 to 12 weeks, these cytokines stimulate a Th-1 dominant cell-mediated immune response, causing an initial influx of CD4 and CD8 lymphocytes and activated macrophages that surround the tubercle bacilli to form granulomas.

The therapy for MTB has not changed over the years and typically involves a 4-drug regimen of isoniazid or ethambutol, streptomycin, rifampicin and pyrazinamide. The therapy is usually over the course of 6 months or until the patient is culture negative on three separate consecutive tests.

References

Author: S. Ranganathan MD, Children’s Hospital of Pittsburgh, Pittsburgh, PA

Contributor: Megan K. Dishop MD, The Children’s Hospital, Denver, CO
Diagnosis: Mesoblastic nephroma (96%)
Alternative terms: congenital mesoblastic nephroma (CMN), classic CMN

Other responses:
- Metanephric stromal tumor (3%)
- Unknown (1%)

Answers to questions:
1. E 25% of respondents (A 0%, B 75%, C 0%, D 0%)
2. C 76% of respondents (A 5%, B 14%, D 2.5%, E 2.5%)
3. A 86% of respondents (B 0%, C 0%, D 6%, E 8%)

Discussion
Mesoblastic nephroma (MN) is a distinctive infantile renal neoplasm composed of monomorphous spindle cells. Although it comprises only 2% to 3% of pediatric renal tumors, MN is the most common renal neoplasm in the first 3 months of life, and is usually discovered before the patient reaches 6 months of age.

MN is generally associated with good outcome, and most cases are treated by nephrectomy alone. However, recurrences and metastases do occur in about 5% of cases. In recent years, a substantial proportion of MNs have been detected during fetal sonography. Hydramnios is common during gestation, and nonimmunologic fetal hydrops is reported. Hyperreninism, hypercalcemia, coagulopathy, and/or shock from tumor rupture during delivery have been reported.

MN arises unicentrically, and usually appears to have arisen deep within the parenchyma near the renal sinus. The renal sinus and adjacent structures on the medial side of the kidney are major sites of extrarenal spread of MN, and surgeons and pathologists must pay particular attention to the medial margin of the resection specimen in order to determine completeness of resection.

The appearance of the sectioned surface is variable. Some specimens have a firm, whorled appearance resembling leiomyoma, but soft, friable tumors are more frequently encountered. Hemorrhage, necrosis, and cyst formation are present in many specimens, and have no prognostic significance.

Microscopically, MN is generally categorized into a “classic” fibromatosis-like type and a “cellular” type resembling infantile fibrosarcoma. Variable combinations of these patterns are often seen, as the cellular pattern commonly arises with a background of the classic pattern. Classic MN is characterized by relatively low cell density, low to moderate numbers of mitotic figures, and irregular tongues of tumor extending radially into adjacent kidney and soft tissue. In addition to frequent involvement of the renal sinus, classic MN also may extend into the perirenal fat, where its advancing edge often shows angiomatous vascular proliferation. Cartilage or other dysplastic changes may be found in the
renal parenchyma adjacent to tumor, sometimes becoming surrounded by tumor. The interdigitating borders of the lesion entrap renal tubules and glomeruli, and the entrapped epithelial cells abutting on tumor often undergo "embryonal metaplasia", producing tall cuboidal to columnar cells that must not be misinterpreted as evidence for WT. Tumors of the pure classic pattern are usually small, with nephrectomy specimens rarely exceeding 100 grams.

In contrast, cellular MN is characterized by densely packed spindle cells with a high mitotic rate. Composite specimens, composed of mixed cellular and classic patterns, are not uncommon. Because cellular foci grow faster than those of the classic pattern, they will eventually become the dominant component. Remnants of the classic pattern at the periphery of cellular MNs may be interpreted as a reactive pseudocapsule. Cellular MN can have an interdigitating border similar to that of classic MN, but as they enlarge, many develop a pushing border. Cellular MN may attain very large size, with nephrectomy specimens sometimes exceeding 1 kg.

Two major histologic subtypes of cellular MN can be identified. The most common of these is a "plump cell" pattern, characterized by large spindled or polygonal cells with abundant cytoplasm and variably enlarged, vesicular nuclei that may contain large nucleoli. These cells may form diffuse sheets or interlacing bundles. The prominent nucleoli and cytoplasm of this subtype and the infantile age at diagnosis can lead to confusion with rhabdoid tumor. The features favoring plump cell MN over rhabdoid tumor are (a) less-invasive tumor margins, with a tendency toward encapsulation; (b) predominantly spindled cells; (c) usual absence of cytoplasmic inclusions. The other, less commonly encountered histologic subtype of cellular MN is one that can be described as a "blue cell" variant, closely resembling infantile fibrosarcoma. The sarcomatous appearance of cellular MN does not necessarily imply a high likelihood of recurrence or metastasis if the lesion is completely resected, and the vast majority of cellular MNs are cured by nephrectomy alone.

Immunohistochemical stains are of limited value in the diagnosis of MN. The cells of MN stain in a fashion consistent with myofibroblastic or smooth muscle cells. Ultrastructural studies reveal features consistent with fibroblasts or myofibroblasts. Abundant rough endoplasmic reticulum (RER) with branching and anastomosing profiles are a prominent feature in most specimens, and primitive cell junctions are often found.

MNls lack the abnormalities in chromosome 11 that characterize Wilms tumor and are associated instead with polysomies for chromosomes 8, 11, 17, and 20. Cellular MN is associated with the t(12;15)(p13;q25) translocation, which results in the ETV6-NTRK3 gene fusion. This is the same genetic abnormality that is found in infantile fibrosarcoma, supporting the notion that these two tumors represent a single biologic entity.
The differential diagnosis of renal tumors in infants includes primarily MN, Wilms tumor (WT), and malignant rhabdoid tumor (RT). Other rare tumors in infancy include clear cell sarcoma of the kidney (CCSK), metanephric stromal tumor, and ossifying renal tumor of infancy. Although MN is the most common renal tumor in infants less than 3 months of age, WT is the most common tumor beyond 3 months of age, making it the most common renal tumor in infancy. WT often contains a stromal component generally similar to that seen in MN, however the presence of blastemal and/or epithelial elements easily distinguishes WT from MN. WT also typically produces a tumor capsule which produces sharp circumscription from the surrounding non-neoplastic kidney, whereas MN shows an irregular interface with entrapment of normal tubules and glomeruli. RT is distinguished from MN by its lack of spindled cells, presence of prominent nucleoli, eosinophilic cytoplasmic globules, loss of nuclear INI1 expression, and predilection for angioinvasion and/or metastatic disease. CCSK is an aggressive lesion of the kidney with cells showing nuclear clearing, and differs from MN by its complex “chickenwire” vascular network. Occasional prominent vascularity in MN may cause confusion with CCSK, but the chromatin of MN cells is coarser than CCSK. Desmin and actin expression in MN also distinguishes it from CCSK. Metanephric stromal tumor (MST) is a tumor of young children (average age, 2 years) and has overlapping histologic features with MN, including predominance of spindle cells and lack of encapsulation. Alternating regions of hypocellular myxoid or sclerotic tissue and hypercellular fibroblastic tissue are characteristic. Concentric collarettes of stromal cells surrounding either tubules or vessels, similar to that seen in renal dysplasia, and angiodysplasia of intratumoral arterioles are other typical features.

References:

Author: Marina Landa MD, Children’s Hospital of Michigan, Detroit, MI

Contributor: Megan K. Dishop MD, The Children’s Hospital, Denver, CO
2009-13

**Diagnosis:** Giant cell angiofibroma (63%)

Alternative terms: Solitary fibrous tumor, hemangiopericytoma, hemangiopericytoma-solitary fibrous tumor with giant cells, giant cell angiofibroma-SFT

Other responses:
- Giant cell fibroblastoma (25%)
- Giant cell fibroblastoma vs. dermatofibrosarcoma protuberans (2%)
- Dermatofibrosarcoma protuberans (5%)
- Benign fibrous histiocytoma (4%)
- Spindle cell lipoma (1%)

**Answers to questions:**
1. E 95% of respondents (A 3%, B 1%, C 1%, D 0%)
2. A 81% of respondents (B 4%, C 5%, D 0%, E 1%)
3. C 100% of respondents (A 0%, B 0%, D 0%, E 0%)

**Discussion:**
This left eyebrow cystic lesion is characterized by very thin encapsulation. It is well-circumscribed and shows several solid spindle cell areas and slit-like vascular areas. The background matrix shows foci of dense collagen. The lesional cells are medium-sized and angular, with indistinct cytoplasm and small nuclei. There are scattered mitotic figures. Multinucleated giant cells are scattered throughout, especially around dilated vascular spaces, typical of giant cell angiofibroma.

First described by Del Tos in 1995, giant cell angiofibroma (GCA) is a distinctive benign mesenchymal tumor usually occurring in the orbital region and eyelids.\(^1,2\)

Although originally thought to be a lesion exclusively occurring in adult males, it is being recognized more in younger individuals and without gender predilection. GCA also has a wider anatomical distribution than was originally documented, and has been reported in the head and neck region (intra-oral, scalp, face, neck, submandibular, retroauricular region), mediastinum, scapular region, thigh, back, retroperitoneum, vulva, and other sites. Men tend to present with orbital lesions, whereas women tend to present with extra-orbital lesions. Typically, patients range in age from 18 to 81 years, with a median age of 45 years. Clinically, these lesions are typically slow-growing, sometimes painful, lesions. Average diameter is 3 cm. Although benign, there are reports of recurrence after incomplete excision.

GCAs are typically well-circumscribed lesions, and some are also encapsulated. The hallmark morphologically is the prominent vascularity, the spindle cell background, and the “patternless pattern” that is typical of a solitary fibrous tumor. Floret-type giant cell are usually plentiful. Some lesions may show alternating hypocellular and hypercellular areas. Stag horn-type pericytomatos
patterns are typically seen. There are cases where the collagen is very thick, hyalinized, and in bands, giving an overall nodular pattern to the tumor. Some authors believe that this lesion may represent a giant cell rich variant of a solitary fibrous tumor. The giant cells may be large in number and diffusely distributed or they may be scarce and limited to the richly vascularized areas and loose stroma. The giant cells may show multiple central nuclei or they may have a peripheral wreath-like arrangement. Interstitial lymphocytic and monocytic cells may be noted. Mitotic figures are not abundant. The lesional cells show strong positivity to CD34, CD99, vimentin, and less frequently bcl2. No reactivity has been identified with desmin, muscle specific actin, c-kit, or inhibin. Rarely, it may show features of Schwannian differentiation.

There is considerable overlap in morphology with solitary fibrous tumor, giant cell angiofibroma, and giant cell fibroblastoma (GCF). Both GCA and GCF have pseudovascular spaces which are lined by multinucleate giant cells and both are CD34-positive, suggesting that these tumors may be closely related. GCF more commonly involves the dermis, and is most common on the trunk rather than the orbital region. The distinction morphologically is that GCF is more infiltrative, has less cellularity overall, and less conspicuous vasculature than GCA. GCF has a biologic relationship to dermatofibrosarcoma protuberans (DFSP), both associated with a derivative chromosome involving chromosomes 17 and 22. It is unknown whether GCA shows a similar cytogenetic abnormality, although it should be noted that there has been a report of GCA with synchronous dermatofibrosarcoma protuberans (DFSP) areas. Pleomorphic hyalinizing angiectatic tumor may also be closely related to GCA, although this is usually a lesion occurring in older patients and has considerable atypical features.

References:

Author: Vinay Prasad MD, Nationwide Children's Hospital, Columbus, OH

Contributor: Anita Sengupta MD, University of Pennsylvania, Philadelphia, PA
Diagnosis: Thrombotic microangiopathy (98%), associated with post-streptococcal glomerulonephritis

Alternative terms: Microangiopathic hemolytic anemia, Hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), TTP/HUS.

Other responses:
- Hemolytic anemia (1%)
- Unknown (1%)

Answers to questions:
1. B 83% of respondents (A 4%, C 2%, D 0%, E 11%)
2. E 84% of respondents (A 1%, B 11%, C 3%, D 1%)
3. A 89% of respondents (B 2%, C 1%, D 8%, E 0%)

Discussion:
The digital images of the patient’s peripheral smear display characteristic features of microangiopathic hemolysis, namely, fragmented, misshapen red blood cells that have been termed schistocytes (derived from the Greek schistos, meaning cleft, or split) due to fragmentation that has occurred as the red cells attempt to navigate the damaged microvascular circulation. Regardless of their specific etiology or pathogenesis, schistocytes are the pathologic hallmark of the thrombotic microangiopathies (TMAs), encompassing those conditions with common features of occlusive microvascular thrombi, platelet aggregation with marked thrombocytopenia, and fragmentation of red blood cells (which, when combined with clinical and laboratory indicators of hemolytic anemia, is described as microangiopathic hemolytic anemia [MHA]). Traditionally, the TMAs have been divided into thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), two disease entities whose apparent clinical and laboratory similarities belie their distinct pathogeneses. However, with increasing knowledge regarding the mechanisms responsible for the various TMAs, the broad subtypes of TTP and HUS have been further subcategorized to include the familial/congenital and idiopathic acquired forms of TTP (i.e., the ADAMTS-13-deficient types), as well as the secondary forms of TTP; the diarrhea-associated (typical) and diarrhea-negative (atypical) forms of HUS; and the TMAs complicating the use of calcineurin inhibitor (i.e., cyclosporine, tacrolimus) and other medications.

The clinical presentations of TTP and HUS, while classically distinct, may in some instances be so similar and with so many overlapping features as to render them indistinguishable by clinical criteria alone. In the landmark paper written in 1966, Amorosi and Ultmann described a clinical diagnostic pentad for TTP, consisting of thrombocytopenia, MHA, neurologic signs and symptoms, renal dysfunction/failure, and fever. However, in reality, the classic pentad is observed only in a minority of patients. Furthermore, with the advent of therapeutic plasma exchange (TPE) in the late 1970s – which dramatically reduced the mortality of
TTP from 85-100% to 10-30% – it became apparent that less stringent clinical criteria were necessary in order to provide the maximal potential therapeutic benefit of TPE for patients who might actually have TTP. Therefore, the pentad has evolved into a less restrictive triad of thrombocytopenia, schistocytosis/MHA, and increased serum lactate dehydrogenase (LDH), reflective of both hemolytic and ischemic injury to the red blood cells. HUS is a TMA that traditionally has been separated from TTP by the presence of acute renal failure and by the association with diarrheal illness caused by one of the Shiga toxin-producing enterohemorrhagic bacteria (“typical” HUS, accounting for ~95% of cases), the best known of which is the O157:H7 serotype of Escherichia coli. The less common nondiarrheal form of HUS (~5% of cases; “atypical HUS”) has been ascribed in part to deficiencies in regulatory proteins involved in the alternative complement pathway. Clinical overlap may exist, as some patients with ADAMTS-13 deficient TTP present with marked renal insufficiency, and some with Shiga toxin-associated diarrheal HUS manifest neurologic deficits and even show some response to TPE.

In order to place the TMAs in their proper clinical and pathophysiologic perspectives, it is helpful to review the underlying mechanisms involved in the formation of microvascular thrombi, beginning with the role of ADAMTS-13 in the processing of von Willebrand factor (VWF), since defective cleavage of VWF is the common end-result of the ADAMTS-13-deficient forms of TTP. In 1982, Moake et al reported 4 patients with chronically relapsing TTP who had “unusually large” (UL) VWF multimers in their plasma samples; these large multimers were believed to be due to defective VWF processing. In fact, cumulative evidence has established that ULVWF multimers are responsible for the pathologic platelet adhesion and aggregation in TTP. In normal healthy individuals, VWF is synthesized predominantly within endothelial cells (and, to a lesser extent, within megakaryocytes), where monomers are linked by disulfide bonds to form high-molecular weight multimers that may attain a weight of millions of Daltons. The ULVWF multimers are stored within the Weibel-Palade bodies of the endothelial cells, which, when stimulated, secrete the multimers in the form of “long strings” that remain attached to the endothelial cell membrane but also adhere to the glycoprotein 1bα components of the platelet glycoprotein 1bα-IX-V surface receptors. The platelets, in turn, adhere to each other by the activated glycoprotein I Ib-IIIa receptors, thus generating platelet aggregates, which produce the occlusive platelet-rich microthrombi. However, the potentially deleterious effects of these microthrombi are preempted by the presence of a specific VWF-cleaving protease that circulates in normal plasma and cleaves the sticky long VWF multimer strings as they are secreted by the endothelial cells (specifically, at an exposed 1605Tyr-1606Met peptide bond in one or more of the susceptible A2 domains of the VWF monomeric subunits). This VWF multimer cleavage process is believed to be most efficient in the setting of high fluid shear stress (flow). It was long suspected that either a deficient or defective VWF-cleaving protease was ultimately culpable for the inability to cleave the long VWF multimers upon their release from the surfaces of stimulated endothelial cells,
thus resulting in uncontrolled platelet aggregation and microvascular thrombosis and precipitating the clinical manifestations of TTP. The specific protease responsible for cleaving the VWF multimer strings was identified in 2001 and was shown to be a member (number 13) of a family of 19 separate metalloprotease enzymes that have been named ADAMTS ("a disintegrin and metalloprotease with thrombospondin-type repeats") and is therefore designated ADAMTS-13. ADAMTS-13 (encoded on chromosome 9q34) is synthesized principally within the liver and is subsequently secreted into the plasma as an active enzyme within seconds to minutes following secretion of the VWF multimer strings.

The discovery of ADAMTS-13 has allowed for the following mechanism-based classification of the TMAs: ADAMTS-13-deficiency (TTP); excess secretion/persistence of long VWF multimer strings (HUS); and inactivation of proangiogenic factors (i.e., vascular endothelial growth factor [VEGF]; transforming growth factor-beta [TGF-β]) (for example, bevacizumab-associated TMA). TTP is further subdivided into familial and acquired forms: in familial TTP, ADAMTS-13 is reduced to <5-10% of its normal plasma level both during and between clinical thrombotic episodes, while individuals with acquired TTP experience a transient decrease in ADAMTS-13 to <5-10% of normal, which subsequently attains normal levels following recovery. The ADAMTS-13 deficiency in the rare familial form of TTP has been linked to mutations in ADAMTS alleles (either homozygous or double heterozygous) on chromosome 9q34. Acquired TTP, in turn, which accounts for the overwhelming majority of cases, has been shown to be associated with IgG autoantibodies that inhibit ADAMTS-13 activity by binding to the spacer portion of the cysteine-rich spacer domain of ADAMTS-13, which functions in docking the protease to the VWF strings.

In contrast to TTP, the thrombotic episodes in HUS are not associated with impaired ADAMTS-13 activity. Rather, the Shiga toxins (Stx-1 and Stx-2) are believed to stimulate rapid and abundant secretion of long multimeric VWF strings from endothelial cells with a predilection for the glomerular capillary endothelial cells. Although ADAMTS-13 levels are normal, their function is impaired by the Shiga toxins, thus resulting in the formation of glomerular microvascular thrombi and acute renal failure. Additionally, inflammatory cytokines, namely, TNF-α, IL-6, and IL-8, also stimulate endothelial cell secretion of long VWF strings, thereby amplifying the effects of the Shiga toxins. The peculiar localization of this process to the renal glomerular microvasculature remains unexplained. While Shiga toxins account for the vast majority of cases of HUS, the rare nondiarrheal forms of HUS have been ascribed in part to deficiencies in regulatory proteins participating in control of the alternative complement pathway (i.e., factor H, factor I, factor B, or cofactor MCPCD46).

Other operative mechanisms involved in the TMAs have also begun to be elucidated. In the case of the calcineurin (protein phosphatase 2B) inhibitors cyclosporine and tacrolimus, the prolonged state of phosphorylation induced by
their biochemical actions is believed to trigger secretion of long VWF strings by endothelial cells, thus overwhelming the cleaving capacity of ADAMTS-13. Bevacizumab, a humanized monoclonal antibody that binds and inactivates vascular endothelial growth factor (VEGF), is felt to bind the renal glomerular podocyte-secreted VEGF, producing a clinical picture resembling HUS. Finally, in preeclampsia/HELLP (hemolysis-elevated liver enzymes-low platelets) syndrome, soluble VEGF receptor-1 and endoglin (which respectively binds and inactivates VEGF and TGF-β-1 and -3) have been proposed either to cause or contribute to the progressive renal dysfunction, hypertension, and hepatic necrosis that comprise the clinical spectrum of this syndrome.

One of the potential means by which the pathologist may assist the clinician in distinguishing TTP from HUS in an individual case lies in determining the composition of the various components within the microthrombi (i.e., the relative percentages of platelets and fibrin). Various diagnostic pathologic methods, including histochemical, ultrastructural, and most recently, immunohistochemical, have been employed to highlight the platelet/VWF-rich nature of the thrombi in TTP, the most recent being the use of anti-CD61 (glycoprotein IIb-IIIa receptor). In contrast, the thrombi observed in HUS, at least in the more common diarrheal form, have been shown to be comprised predominantly of fibrin, with only a paucity of platelets and VWF, and accompanied by prominent endothelial cell swelling. An autopsy study published in 2003 examined 25 cases of TTP and 31 of HUS (56 total), using anti-Factor VIII immunohistochemical staining to identify platelet-rich thrombi and phosphotungstic acid-hematoxylin (PTAH) to accentuate the fibrin component. While the microthrombi in all 25 TTP patients were characterized by abundant Factor VIII expression, supporting a platelet-rich composition, the thrombi in the 31 HUS patients demonstrated prominent PTAH staining and only sparse factor VIII expression, more consistent with fibrin-rich, platelet-poor thrombi. Another difference observed in this study was in the distribution of organ involvement: in TTP, thrombi were most frequent within the heart, pancreas, kidneys, adrenal glands, and brain (in decreasing order), while in HUS, the thrombi were confined predominantly to the kidneys. Admittedly, the findings in this study would be more powerful if they could be replicated in future series, especially those involving living patients, perhaps employing a more comprehensive battery of antibodies for immunohistochemical stains (i.e., anti-CD61, anti-fibrin antibodies); nevertheless, they do offer some promise for differentiating platelet-rich microthrombi from fibrin-rich microthrombi. Indeed, a 2005 autopsy study did employ anti-CD61 and anti-fibrin II as a means for distinguishing TTP from disseminated intravascular coagulation (DIC).

Despite the difficulty in separating TTP from HUS and other TMAs on clinical grounds, significant advances in understanding of the pathogenesis of TTP and HUS have had significant therapeutic implications. Perhaps most importantly, the efficacy of TPE in the setting of acquired TTP, which has been recognized since the late 1970s, is now more completely understood within the context of ADAMTS-13 autoantibody-mediated TTP. Plasma exchange offers the combined
benefit of fresh frozen plasma or cryosupernatant, containing active uninhibited ADAMTS-13, with plasmapheresis, which effectively removes the anti-ADAMTS-13 autoantibodies and the large VWF multimers. The associated inflammatory cytokines that exacerbate TTP episodes by stimulating release of long VWF multimer strings by endothelial cells may also be removed with TPE. It is estimated that up to 80-90% of patients with acquired ADAMTS-13 autoantibody-mediated TTP are able to survive an acute episode of TTP with minimal to limited organ injury. It is for this reason that the clinical criteria necessary for a presumptive clinical diagnosis of TTP have relaxed: by requiring the presence of only thrombocytopenia and MHA (with elevated LDH), TPE can be initiated most expeditiously to the greatest number of potential TTP patients. Additional therapeutic strategies proposed to mitigate the potential damage threatened by TTP include the administration of glucocorticoids and rituximab, as well as splenectomy, to suppress ADAMTS-13 autoantibody production, and the use of purified and recombinant active ADAMTS-13 to provide VWF-cleaving activity.

Somewhat predictably, there is no proven benefit of TPE for those TMAs not associated with ADAMTS-13 deficiency. Thus, in HUS, treatment is primarily supportive, with approximately 40% of affected individuals requiring dialysis for renal failure.

The final issue to address is the presence of the elevated ASO titer in the present case. Although rare, HUS accompanying or later complicating acute poststreptococcal glomerulonephritis (APSGN) has been documented in several case reports. However, the relationship between the two entities is entirely unknown. Interestingly, in these cases, the histopathologic findings noted on renal biopsy were characteristically those of acute proliferative glomerulonephritis and not of TMA, although the clinical and laboratory features were compatible with both APSGN and HUS. It has been postulated that the particular streptococcal serotype (strain) and the unique individual immune response somehow collectively predispose to complement dysregulation and overactivation of complement components, in particular, C3, which has been implicated in cases of nondiarrheal [atypical] HUS).

In conclusion, this case serves to highlight the similarities in clinical presentation among the TMAs, as well as their diverse etiologies. Ultimately, it is hoped that treatments as effective as TPE for the ADAMTS-deficient forms of TTP will be available for the other TMAs as a better understanding of them develops.

References
4. Hosler GA, Cusumano AM, Hutchins GM. Thrombotic thrombocytopenic purpura and
hemolytic uremic syndrome are distinct pathologic entities: a review of 56 autopsy cases. 

Author and Contributor: Michael J. Caplan MD, Mercy Hospital, Cadillac, MI
2009-15

**Diagnosis:** Lymphocytic thyroiditis (93%)

Alternative terms: Hashimoto thyroiditis, Autoimmune thyroiditis

Other responses:
- Papillary carcinoma in Hashimoto thyroiditis (7%)

**Answers to questions**

1. E 88% of respondents (A 9%, B 0%, C 3%, D 0%)
2. E 96% of respondents (A 0%, B 0%, C 0%, D 4%)
3. E 53% of respondents (A 31%, B 4%, C 12%, D 0%)

**Discussion:**

The section corresponds to a lobe of thyroid gland showing exuberant infiltration by mature lymphocytes. There is extensive replacement of the parenchyma with active appearing germinal centers. Variable areas of collapse and atrophy are noted. The residual thyroid follicles show a spectrum of active, regressing and metaplastic changes. Isolated areas show nuclear pseudo-inclusions and variable nuclear clearing, however no conclusive areas of papillary carcinoma are noted. There is no evidence of infiltrative or sclerosing neoplasm or Hürthle cell change, and regional lymph nodes appear reactive.

Chronic lymphocytic thyroiditis represents a form of Hashimoto disease, sometimes described as juvenile variant when it occurs in young people. It is a form of autoimmune thyroiditis that presents with diffuse goiter, sometimes with nodularity and clinical manifestations of hypothyroidism. It occurs more frequently in females and is the most frequent form of goiter in adolescents. The antigenic targets include thyroglobulin, thyroid microsomal antigen, thyroid peroxidase, and thyrotrophin receptor. A significant number of patients have circulating antithyroglobulin antibodies and antithyroid microsomal antibodies.

Important associations of lymphocytic thyroiditis include Sjögren syndrome, chronic active hepatitis, polyglandular autoimmune syndromes, adrenal insufficiency, and Graves disease. Polyglandular autoimmune syndromes usually include endocrine hypofunction. Specifically, PGAS type II may include thyroiditis and hypothyroidism.

The association of papillary thyroid carcinoma with thyroiditis has been both supported and disputed in the literature, including in publications where RET mutations have been documented in CLT. While some regenerative and hyperplastic areas of thyroid gland may look atypical or mimic papillary carcinoma, conclusive evidence rests on findings nuclear overlapping, infiltrative edges and desmoplasia. While C-cell hyperplasia has been reported, there is no particular association with medullary carcinoma.

Thyroid gland lymphomas are typically B-cell neoplasms, including MALT-type...
lymphomas. These tumors usually present as a thyroid mass compressing neck structures. Clinically, there is frequently an association with lymphocytic thyroiditis, more frequently in middle age and older patients. Microscopically, these MALT-type B cell lymphomas are characterized by effacement and replacement of thyroid architecture by the lymphoid process.

References:


Author: Hector Monforte MD, All Children’s Hospital, St. Petersburg, FL

Contributor: Vinay Prasad MD, Nationwide Children’s Hospital, Columbus, OH

**Total number of survey respondents:** 80