

TITLE: Subglottic Stenosis in Wegener's Granulomatosis
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In 1931, Heinz Klinger of the University of Berlin first reported two patients who died having prolonged sepsis with inflammation of blood vessels scattered throughout the body. Five years later, Friederic Wegener in Breslau described a distinct syndrome in three patients. These patients were found to have necrotizing granulomas involving the upper and lower respiratory tract. In 1954, seven more patients were described, resulting in the establishment of the definite criteria for the diagnosis of the disease described by Wegener.

Wegener joined the Nazi Party in 1932. As a high ranking military doctor he spent some of WWII in a medical office near a Jewish ghetto in Lodz, Poland. There is speculation that he participated in experiments on concentration camp inmates. After his Nazi past was discovered in 2000, the chest physician group began a movement to rename Wegener's granulomatosis. Dr. Friederic Wegener died in July of 1990 at the age of 83.

Wegener's Granulomatosis (WG) is a necrotizing granulomatous vasculitis of autoimmune origin. The disease has a predilection for the upper and lower respiratory tracts and the kidneys. In the sinonasal tract, the vasculitis can cause sinusitis, nasal crusting, epistaxis, septal perforation and saddle-nose deformity. In the lungs, the disease may lead to pneumonitis and hemoptysis. In the kidneys, a crescentic glomerulonephritis develops, eventually leading to renal failure. Other manifestations include skin lesions, arthritides, conjunctivitis, and other non-specific systemic inflammatory problems. Subglottic stenosis is a potentially life-threatening manifestation of Wegener's granulomatosis. This narrowing of the upper airway at the level of the cricoid cartilage and/or upper tracheal rings presents a management dilemma.

Subglottic stenosis (SGS) is reported to occur in 16-23% of patients with Wegener's Granulomatosis. (Langford) It has been reported to occur more often in females. (Shokkenbroek, Gluth) The median age at diagnosis is 26. (Langford) and is more likely to occur in patients diagnosed with Wegener's before age 20. (Langford) Patients with WG and SGS tend to have more sinus involvement and saddlenose deformity than other WG patients. On the contrary, SGS patients tend to have less lung and kidney involvement. (Langford)

The pathogenesis is unclear. Subglottic stenosis can progress in the absence of systemic disease. Few patients have WG exacerbations around the time of diagnosis with SGS. In series where patients were followed, need for repeat procedures was not related to repeated systemic disease flares. It is postulated that during flares of systemic disease, subclinical subglottic involvement occurs, which subsequently heals with circumferential scarring. (Shokkenbroek) Some authors speculate that the subglottis is vulnerable because it is a watershed area of the microcirculation. This watershed area is the junction of 2 separate embryological growth centers. (Eliachar) Exposure of respiratory epithelium to gastric contents during LPR episodes is also believed to play a role. (Gluth) Initial granulomatous inflammation is followed by circumferential scarring and airway narrowing.

Dyspnea on exertion is the most common presenting symptom. (79-82%)(Gluth, Langford) Other symptoms include voice change, stridor, or cough. Patients may have a known diagnosis of WG (50%), have other symptoms of systemic disease, or present as a new patient with airway complaints. If the diagnosis of WG is not established, an anti-cytoplasmic antibody assay should be performed. It has been suggested that ANCA titers be performed on nearly all patients with SGS. (Gluth) A positive C-ANCA assay is reported to be 91% sensitive and 99% specific for *active* Wegener's granulomatosis. However, a series of patients with SGS and presumed WG showed that only 57% initially showed a positive ANCA assay. 85% of the cohort eventually became positive at a later date. (Alaani) This emphasizes the fact that SGS can be present in the absence of active disease. It also suggests that ANCA assay be repeated serially if there is diagnostic uncertainty. The presence of ANCA in serum can be detected by indirect immunofluorescence or by radioimmunoassay. Indirect immunofluorescence reveals a pattern of staining that can be more specific for a particular disease. The "cytoplasmic" pattern (c-ANCA) is associated with ANCA reacting with a 29 kD protein from the azurophilic granules of the neutrophil. The "perinuclear" (p-ANCA) pattern is associated with ANCA reacting with myeloperoxidase. Radioimmunoassay of ANCA titers can be used as an initial screening test and to monitor therapy and detect flare-ups of systemic disease. The airway should be fiberoptically examined in the clinic setting. Topical laryngeal anesthesia may be necessary to visualize the subglottic lesion. In the majority of cases (75%), the stenotic segment has the appearance of a mature scar and lacks acute inflammatory changes. (Gluth) CT scans will help to delineate the extent of the lesion but should not be used for primary diagnosis. The stenosis can be graded using the Cotton-Myer classification scheme for grading circumferential subglottic stenosis.

- Grade I - Obstruction of 0-50% of the lumen obstruction
- Grade II - Obstruction of 51-70% of the lumen
- Grade III - Obstruction of 71-99% of the lumen
- Grade IV - Obstruction of 100% of the lumen (ie, no detectable lumen)

Histological proof of WG is obtained by finding vasculitis, necrotizing granulomata and giant cells in biopsy material. But, in general, biopsies of the subglottic lesion are not sensitive for the detection of WG. Only 5-15% of subglottic biopsies performed on patients with positive ANCA titers and SGS return changes consistent with WG. (Gluth, Langford) In contrast, nasal biopsies on a similar cohort of patients yielded 82% sensitivity for WG. (Gluth) Pulmonary function tests are abnormal in 60% of patients with subglottic stenosis. (Langford) Flattening occurs in the flow-volume loop in both the inspiratory and expiratory portions, giving it a box-

like appearance. However, PFTs may not detect less severe stenoses and should never be used for primary diagnosis. An abnormal flow-volume loop is correlated with need for surgical intervention. (Langford)

Treatment of subglottic stenosis should be considered based on the presence of symptoms combined with objective evidence of tracheal narrowing. Other parameters, such as active systemic disease or a change in ANCA titers should never be used as consideration for procedures. Treatment options include immunosuppression, tracheostomy, endoscopic dilation, intralesional steroids, laser procedures, cold knife lysis, open surgical procedures, and airway stents.

Drugs such as corticosteroids, cyclophosphamide, and azathioprine has revolutionized the treatment of WG, with a dramatic reduction in mortality. However, subglottic lesions are generally unresponsive to systemic agents. 49% of SGS cases are diagnosed while a patient is on active therapy. (Langford) Success rates of medical therapy in relieving the obstruction vary from 22%-26%. (Gluth, Langford)

Life-threatening airway obstruction may require tracheostomy as a temporizing or permanent measure. Tracheostomy is necessary in 8 - 60% of cases. (Langford, Schokkenbroek, Gluth, Alaani) Often, success of other therapies is measured by decannulation of the tracheostoma.

Endoscopic procedures have been variably successful at managing this airway lesion. Dilation tracheoscopy can be performed using a Groningen optical dilatation tracheoscope (Karl Storz 1033R)(Fig 1) fitted with a 30 cm Hopkins telescope. Under general mask anesthesia, the scope is introduced. The beveled, fenestrated tip is designed to ensure ventilation as the scope is advanced through the stenosis. The conical design allow the scope to be advanced up to its wider portion. The scope is left in place for 5 – 10 minutes. Dilation tracheoscopy has been shown to be effective the majority of the time for Cotton-Meyer grade I-II in the short term. Repeat procedures are commonly necessary. No complications have been reported with this procedure. The small number of reported cases (9) should be considered. (Shoekkenbroek)

Traditional dilation techniques, combined with intralesional steroid injection have been reported. Under suspension laryngoscopy and spontaneous ventilation, graduated dilators are used to dilate the trachea. Next, methylprednisolone injections are performed in a 4-quadrant, submucosal pattern. Perioperative, systemic steroids are also used. 20 patients received this treatment and were followed for a median of 35 months. The median number of treatments required was 3. Six patients required only 1 procedure. One patient required 22 procedures.. All patients who began therapy with a tracheostomy were eventually decannulated. No patients required a new tracheostomy.

In another series, 21 patients with WG and significant SGS were studied. These patients were treated with intralesional steroid injection combined with mechanical dilation and cold-knife lysis of the lesion. Under suspension laryngoscopy and jet ventilation, methylprenisolone was injected submucosally in 4 quadrants. Lysis of the stenotic ring was then performed by making radial incisions with a laryngeal microsickle knife. The stenosis was then serially dilated with Maloney bougies or a Foley catheter. Topical mitomycin C was variably used. (Hoffman)

Patients with prior procedures (mostly laser) averaged more procedures to obtain adequate airway patency and with a shorter interval between procedures. The authors comment that, subjectively, lesions seen in patients who had undergone prior laser procedures were severe, extensive, and thickly fibrotic. No new tracheotomies were necessary in either group. (Hoffman) The most difficult lesions were found in the 6 patients with prior tracheotomies, presenting with multilevel stenoses, cicatrix formation, vocal cord fixation and arytenoid damage. In these patients, widening of the subglottic region alone was not sufficient. 4 of the 6 patients achieved decannulation by means of various laryngotracheoplastic techniques which were not specified. The authors comment that laser procedures cause extensive scarring and thus patients are more difficult to manage afterward. However, these patients may represent a cohort with more severe disease, who would be more difficult to manage anyway. There is no way to differentiate whether the scarring is from prior laser procedure, or from more extensive inflammation in the airway .

Although abhorred by other authors, laser treatment of SGS has been performed and reported on. For lesions close to the vocal cords, in 2 patients, CO2 laser was used with microsuspension laryngoscopy to resect the stenosis. For lesions far from the cords (>1 cm), in 3 patients, Nd:YAG laser was used with through a fiberoptic bronchoscope, under local anesthesia. (Shvero) 4 out of these 5 patients are reported to have favorable outcomes or decannulation during their follow up period of 6-60 months. However, all patients required multiple treatments (2-18) In addition, one patient required placement of a subglottic stent. (Shvero)

Open surgical procedures have been performed with success. Most commonly performed is the laryngotracheal reconstruction with costal cartilage graft (LTR). It is recommended to defer LTR until a patient is in a quiescent phase of the systemic disease. This should be monitored by serum ANCA titers, CRP, and ESR. It is also recommended that surgery be deferred until a patient is not actively taking steroids or other immunosuppressant medications. (Gluth) A small series of Wegener's patients who received laryngotracheal reconstruction for SGS shows excellent results. 6 of 6 patients were decannulated from their tracheostomy after the LTR. There were no cases of graft failure even in 3 of the patients in whom reactivation of systemic WG occurred. 1 complication of graft displacement occurred. (Gluth)

The use of airway stents to maintain airway patency in SGS and WG is controversial. Some authors have advocated deployment of a Nitinol (nickel-titanium alloy) expandable stent into the subglottic airway when all other therapies fail. Similar stents have been used with success in the distal tracheobronchial tree. A case report exists in the literature. A patient was followed for 48 months after deployment of a nitinol stent. She had a patent airway, no complications, and no ingrowth of granulation tissue. (Watters) Other authors argue that the long-term safety and efficacy of these stents has not been well established. They argue that these devices are associated with stent fracture, migration, increased granulation tissue, and even death. Stents in the subglottis also undergo movement with swallowing and saliva exposure. These factors preclude early mucosalization of the stent, as occurs in more distal portions of the airway. The foreign body reaction, it is argued, causes more granulation tissue ingrowth. (Mair-anecdotal) The argument against stents is further supported by the fact that an emergency trachotomy in the setting of a subglottic metal stent is very difficult to perform.

Based on the published research, the following treatment plan should be followed. If the airway is tenuous, perform emergent tracheotomy. If patient is stable, perform PFTs, CT scan, and fiberoptic endoscopy. 1st line therapy should be endoscopic dilation. With subsequent dilations, cold-knife lysis, and intralesional steroids should be added. Patient should be followed every 3 months with repeat fiberoptic exams and PFTs. Serial ANCA titers are not necessary from an ENT standpoint, since they correlate poorly with SGS progression. Endoscopic procedures should be repeated as necessary. If endoscopic procedures must be performed at an increasingly more frequent interval, consideration should be given to open laryngotracheal reconstruction. Subglottic stents should be avoided if at all possible.

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Idiopathic Midline Destructive Disease

Today's Grand Rounds is a fine discussion of the incidence and treatment of subglottic stenosis occurring in patients who suffer from idiopathic midline destructive disease. One may infer or doubt a causative relationship based on data regarding the absence of granulomatous histology in the stenosis itself, or by the association of positive C-ANCA titers in cases of stenosis occurring in the absence of clinical midline destructive disease.

The taxonomy of idiopathic midline destructive disease has not benefited from the attempts to identify and classify its variants, based on etiology (autoimmune, infectious, neoplastic), histology, clinical manifestations, responses to therapy (microbial, corticosteroid, chemotherapeutic, ionizing radiation) and natural history (remittent, inexorable progression, lethal).

A brief walk through the medical literature yields a collection of terms including polymorphic reticulosis, lethal midline granuloma, malignant midline reticulosis, natural killer-cell lymphoma, peripheral T-cell lymphoma, Wegner's granulomatosis (limited type – without renal disease, and classical type – with renal disease), angiocentric T-cell lymphoma, and idiopathic midline destructive disease.

While the eponymic "Wegener's granulomatosis" serves the vulgate, the inclusive "idiopathic midline destructive disease" will point to the disorder as a challenge to the therapist and not merely a diagnostic dead end with ineluctably hopeless prognosis.

The term "idiopathic midline destructive disease" can be considered as a collection of vectors in which every manifestation of the disease (clinical, histologic, course, etc.) is represented by data types appropriate to that manifestation (continuous, discrete, Boolean, or null). The individual patient can be mapped onto the N-space such that cluster analysis leads to a rational nosology permitting an enlightened pathophysiologic understanding of this (group of) disease(s).

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