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Nine Patients with Chronic Granulomatous Disease Having Selective Neck Dissection for Severe Cervical Lymphadenitis

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Keywords

selective neck dissection; chronic granulomatous disease; gene defects; NADPH oxidase; lymphadenectomy

Introduction

Chronic Granulomatous Disease (CGD) is a rare, inherited disorder due to either X-linked or autosomal recessive defects of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, compromising the ability of phagocytes to produce reactive oxygen species.^{1, 2} The prevalence of CGD in Europe and the US is around 1:100,000–1:200,000.^{3, 4} CGD patients typically suffer from recurrent bacterial and fungal infections and often develop lymphadenitis, which may suppurate in nearly 60% of patients.^{4, 5, 6} Mouy et al. reported that 73% of their patients had at least one episode of lymphadenitis requiring antibiotics,

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with surgical drainage for those that failed to respond. Due to the multinodal and necrotic nature of their infections, cervical lymphadenitis treated with incision and drainage alone is usually recurrent. The management of severe necrotic CGD cervical lymphadenitis has not been defined in the literature.⁷ We present the initial outcomes of a nine patient series from the NIH in which lymphadenectomy and/or selective neck dissection was used to treat severe necrotic primary or recurrent cervical lymphadenitis.

Materials and Methods

Ethical Consideration & Study Design

In this retrospective case series, patient data were obtained from hospital records of 194 CGD patients at the Clinical Center of the National Institutes of Health (NIH; Bethesda, Maryland) from 1999 to 2008. All patients were consented to NIH IRB approved protocols (93-I-0119 or 05-I-0213).

The nine patients presented this study had CGD confirmed by molecular and/or functional testing. Cervical lymphadenitis with necrotic abscesses was determined by clinical evaluation and radiological imaging to require surgical lymphadenectomy. Refractory cervical lymphadenitis was determined by persistence or recurrence of local disease. Microbiology evaluation was performed on all specimens but not all samples were culture positive, and not all cultures necessarily represent likely pathogens (e.g., *Corynebacteria*). In fact, most organisms encountered in CGD lymphadenitis are not intrinsically resistant but because of local factors, including necrosis, do not clear with antibiotics therapy alone. Empirical therapy for culture negative lymphadenitis included high-dose trimethoprim-sulfamethoxazole, a fluoroquinolone and an agent active against *S. aureus* (e.g., vancomycin or oxacillin). Failure to resolve and nodal abscesses were indicators for surgery. Surgical excision and/or selective neck dissection of one or more anatomic neck levels(s) affected by CGD pathology, with preservation of muscles, nerves and blood vessels of the neck were performed as defined in the AHNS/AAO-HNS classification.⁸

Results

Patient Characteristics

Table 1 summarises general characteristics of the series. Nine patients with severe or recurrent multinodal lymphadenitis requiring excisional lymphadenectomy were identified (4.7% of the total CGD population). Most patients were male (7/9), with the most common X-linked genotype, gp91^{phox} deficiency, as expected. The two female patients had p22^{phox} and p47^{phox}, respectively. The average age at first surgery was 20 years (range: 10–40 years).

Microbiology

The most common cultured organisms from surgical specimens included *S. epidermidis* (n=8), *S. aureus* (n=6), and *Actinomyces sp.* (n=3), which are commonly recovered from CGD patients^{5, 6}. (Table 1) Staphylococci were present in 15/26 surgical cultures. All nine patients were on standard CGD antibiotic prophylaxis (trimethoprim-sulfamethoxazole and

itraconazole +/- interferon gamma) prior to admission (Table 1). Antibiotic therapy was based on culture results when available. Most patients received intravenous antibiotics for the lymphadenitis, but had persistent abscess formation and necrotic tissue, leading to surgery

Radiologic Evaluation and Pre-operative Planning

Computed tomography (CT), magnetic resonance (MR) imaging scans, ultrasounds, and x-rays were used to evaluate lymphadenopathy. A total of 54 CT scans were used in pre- and post-operative planning. These scans guided whether lymph node excision or more extensive surgical approach were used. As our surgical approach evolved, the extent of surgery was based on the necrotic appearance and the number and level(s) of enlarged lymph nodes visible on scans (Figure 1). Of the fourteen selective neck dissection procedures, all had evidence of necrotic or multiple nodal involvement on pre-operative CTs, and the majority of the scans (71%) had both. However, the area of disease ranged widely within this series and selective neck dissection was not performed when the disease was localised.

Surgical treatment

Table 2 describes the extent of cervical disease and surgical treatment. The nine patients in this series underwent 26 surgical neck procedures. The distribution of initial or recurrent lymphadenopathy or abscessed lymphadenitis included 14 cases in the left neck, 7 in the right neck, 3 on both sides, and two central neck lesions (anterior to hyoid cartilage or submental lymph nodes). Most patients underwent a level II lymph node dissection (n=14, 54%) followed by surgery at level III-V (Level III n=6, Level IV n=6, Level V n=7). The average number of surgeries per patient was 2.88 (range:1–6). The average days to disease recurrence for all patients post-surgery was 450 days (range: 31–1,849 days).

Patients who required repeat surgeries had often received more limited surgical treatment initially, such as local lymph node or level excision (Patients 1, 4, 5, 6, 7, 9). After observing recurrences adjacent to excisions in several patients, we altered our approach to incorporate selective neck dissection to address the multi-nodal and multi-level nature of the infection. For instance, four patients treated by selective neck dissection of levels I-V initially (patients 3 and 8) or after recurrences (Patients 6 and 7) remained disease free in the levels dissected during follow up. Patients who recurred did so in remaining nodes at the margins of the dissection (Patients 1, 4, 5, 6, 9). Overall, 46% of patients undergoing limited excision at initial surgery had ipsilateral recurrence, while 38% of patients who underwent wider selective neck dissection had ipsilateral recurrence with the same organism, underscoring the multi-nodal nature of infection in these patients appreciated in Figure 2.

Surgical complications and their prevention

In our series there were no mortalities related to surgery. Due to the anatomical location of most lesions involving the jugulodigastric nodes in level II, nerve monitoring was routinely done for the marginal branch of the facial nerve, and to identify the spinal accessory nerve intra-operatively. Temporary nerve praxis of the marginal branch of CN VII occurred in 2/26 instances. In patient 4, who underwent a bilateral selective neck dissection and lymphadenectomy, there was anticipated nerve involvement due to the location of diseased

tissues. Patient 6 experienced unilateral lower lip weakness following a selective neck dissection of Level II-V. Function returned in both patients within 48 hours. Blood loss during the procedures ranged from minimal to 500 ml. The majority of cases (n=21, 81%) had minimal blood loss (<50 ml). There were no cases of postoperative bleeding or hematoma/seroma formation. Only 1/26 operative case required the sacrifice of the internal jugular vein, in order to remove inflamed lymph nodes while completing the inferior left neck dissection (level IV).

Because of propensity for granuloma formation with braided sutures, full thickness inverted vertical mattress sutures with nylon monofilament in a single layer were used for closure and left in place for ~two weeks. Additionally, all patients receive post-operative steroids to facilitate healing, a relatively unique aspect of CGD wound healing. Two patients developed extremely pronounced or visible scars due to this impaired wound healing.

Discussion

Synopsis of approach

First pioneered by Bocca, Gavilan and other surgeons for cancer, selective neck dissection conserves unaffected structures and function while still providing comprehensive lymphadenectomy for affected or at-risk nodes. Due to the multi-focal nature of bacterial lymphadenitis in CGD, we adapted this surgical approach to address the level(s) of nodal involvement. This surgical approach incorporated principles from oncology to CGD patients and evolved after recognizing the patterns of recurrence in this patient population.

Strength study and comparison to other studies

To date, literature on CGD and surgical management of antibiotic resistant cervical lymphadenitis is limited primarily to single case discussions. A slightly larger case series study (n=10) examining all surgical procedures on their patients included incision and drainage of abscesses, thoracentesis and bronchoscopy. The surgical complications and challenges of CGD were discussed.⁹ Lublin et al, completed one of the most comprehensive studies on liver surgery in CGD (n=22 patients with 61 liver abscess surgeries). However, they focused on surgical liver abscess incision and drainage.¹⁰

The majority of patients with CGD will experience lymphadenitis. When an organism is not found, trimethoprim-sulfamethoxazole, a penicillinase-resistant penicillin and a fluoroquinolone are usually given. If nodal abscesses develop, surgical excision should be pursued.

Our surgical approach to these patients has evolved based on our experience with recurrence. With this newer and initially more aggressive approach using selective neck dissection we have improved disease control as well as functional and cosmetic outcomes. Through this approach, we observed a reduction of reoccurrence within the region undergoing selective neck dissection. Although an effective surgical treatment strategy emerged within our patient population, the cohort is too small for statistical validation, due to the rarity of the disease. Increasingly longer times between neck pathology recurrences suggest that the advent of better surgical approaches and better medical management have had benefits.

Conclusions

Our experience with this patient group demonstrates that selective neck dissection in CGD patients decreases the recurrence of neck pathology. Head and neck surgeons should be aware of the potential for adapting surgical approaches developed for multi-nodal disease to treat the pathology adequately while preserving functional and cosmetically acceptable outcomes.

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Five Key points

1. Chronic Granulomatous Disease (CGD) is a rare, inherited disorder due to an X-linked or autosomal genetic defect, in which patients experience a high rate of lymphadenitis.
2. To date, no studies have examined the best treatment for severe lymphadenitis in this patient population.
3. We present a nine CGD patient retrospective case series, examining surgical treatment of cervical lymphadenitis.
4. Our evolving surgical strategy shows that an initially more aggressive surgical approach (selective neck dissection) can help prevent recurrent infection.
5. The results found within this patient population may be relevant to other multi-nodal disease, including cancers of the head and neck region, while preserving functional and cosmetically acceptable outcomes.

Figure 1. CT Neck (Axial 2.5 mm sections from oropharynx through sternal notch)

CT Axial 2.5 mm sections from oropharynx through sternal notch of 12-year-old male CGD patient. Shows left level II multimodal involvement including enlarged 1.5 cm necrotic node deep to left sternocleidomastoid muscle.

Figure 2. Intra-operative photos

Intra-operative photos showing right selective neck dissection with complete lymphadenectomy and preservation of the sternocleidomastoid muscle (A), external jugular vein (B), and spinal accessory nerve (C).

Table 1

Patient Characteristics and Microbiology Results

Patient/ Gender/ CGD Type	Age at surgery	Organism	Prophylactic antibiotics	Antibiotic treatment	Extra-cervical involvement
1 Male gp91phox	25	S. Aureus	B, I	Van	Liver abscesses, mediasternal lymphadenopathy
	25	No growth	B, I	Van, Lin	
	25	No growth	I, Lin	Van, I, B	RLL PNA
	26	No growth	B	Van, Cef	S. Aureus conjunctivitis
	29	S. Aureus	Dox, Lin, I	Van, Leva	RML PNA (Klebsiella)
	31	S. Aureus	Lin, I	Van, C	
2 Male gp91phox	18	Actinomyces, P. magnus	B, C, I	B, Cef, Una, Van	Left lung abscess, aspergillosis
3 Male gp91phox	18	S. Aureus	B, I	B, Mer, Lin	Multiple PNA, TB
4 Male gp91phox	39	Gram (-) rod	Az, B, Mox, Vor	Mer, Dox	Mediastinal lymphadenopathy, multiple PNA, liver abscess
	40	Staph. Epi	B, Dox, Vor	B, Dox, Vor	
	40	Staph. Epi, strep sanguinis	B, Dox	Lin	
	40	Staph spp., gram(-) rod	Dap	Mer, Dap	Wound infection (Candida)
	40	P. acnes, gram(-) rod	I, Dox	I, Dox	
	40	Staph Epi	B, I	Lin	Left axillary dissection
5 Male gp91phox	10	Corynebacterium, Actinomycoses	I, C, F	Pen, F, Cef, Lev, Mer	RUL PNA, osteomyelitis, perirectal abscess
	12	Staph. Epi	I, C, F	Lin	
	13	Staph Epi	I, C, Met	Lin	
6 Female p22phox	23	Staph. Epi, Corynebacterium	Cef, Lev, Clind	Clind, Cef, Rif, Lev	Brain and liver abscesses, aspergillus PNA
	25	S. Aureus	B, I	B, Naf, Van	
	28	Staph Epi	B, I	Pen, Van	Lung abscesses, tubo-ovarian abscess
7 Male gp91phox	12	Staph Aureus	B, F, Leva	Leva, B, Lin	Colitis, perirectal abscess, PNA, mediastinal LAD
	14	Polymicrobial	F, Lev, Vor	Mer	
8 Female p47phox	19	Actinomyces, odontolyticus	Lev, I	Van, Lev, Clind, Pen, Imi	PNA, skin abscesses, impetigo
9 Male gp91phox	16	No growth	B, I, F	B, I, Aug	RML infiltrate, PNA, skin infection, stepmyelitis, sporthrix infection
	18	No growth	B, Leva, F	B	Groin mass
	20	Staph Epi	B, Vor, Leva	B, Vor, Leva	Fungal PNA

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Abbreviations: Aug, Augmentin; Az, Azithromycin; B, Bactrim; Dox, Doxycycline; Dap, Daptomycin; C, Ciprofloxacin; Cef, Ceftriaxone; Clind, Clindamycin; F, Flagyl; Imi, Imipenem; I, Itraconazole; Mer, Meropenem; Met, Metronidazole; Mox, Moxafloracin; Naf, Nafcillin; Leva, Levofloxacin; Lin, Linezolid; Pen, Penicillin; Rif, Rifampicin; Una, Unasyn; V, Van; Vor, Voriconazole

Table 2**Surgical Approach and Days to Recurrence**

Patient /Case	Date of Surgery	Extent of disease	Surgical approach	Time to recurrence (days)
1	A	26/03/00	R+L Level II LN Abs	n/a
	B	20/06/00	L Level II LN Abs	86
	C	21/07/00	L Level II/III LN Abs	31
	D	15/12/00	L Level IV LN Abs	147
			R Level V LN Abs	
	E	23/08/03	L Level I LN Abs	981
F	13/10/05	L Level IV Abs	L Level IV SND	782
2	23/01/01	Ant Neck Abs	Ant Neck Ab Excision	n/a
3	03/07/02	R Level I/II LN Aden	R SND Level I-IV	n/a
4	A	29/08/03	L Level III/IV LN Aden	n/a
	B	10/06/04	L Level III LN Abs	286
	C	06/01/05	L Level I LN Aden	210
	D	10/03/05	Ant + R Neck Abs	63
	E	16/06/05	R Level III LN Aden	98
	F	14/11/05	R Level III LN	151
5	A	08/07/03	L Level I LN	n/a
	B	18/11/04	L Level II LN Aden	499
	C	03/03/05	L Level V LN Aden	105
6	A	20/05/99	L Level II LN Aden+Ab	n/a
	B	21/10/01	L Level II-V Abs+LN Aden	876
	C	11/06/05	L Level I Ab + R Level V Ab	1849
7	A	14/04/05	Left level II and V lymphadenopathy	n/a
	B	14/09/06	R Level II+V LN Aden	518
8	01/06/01	Level II-V LN Aden + R Ab	R+L SND Level II-V	n/a

Patient /Case	Date of Surgery	Extent of disease	Surgical approach	Time to recurrence (days)
9 A	11/08/00	Level I Submental LN Aden	Submental LN Excision	n/a
B	05/09/02	Level I-II R Abs+LN Aden	R SND Level II + Excision SMG	755
C	10/06/04	R Level I Ab	R Ab Excision	644

Abbreviations: L, Left; R, Right; Abs, Abscesses; Ab, Abscess; Aden, Adenopathy; LN, Lymph node; SMG, Submandibular Gland; SND, Selective Neck Dissection