

Megaesophagus and Esophageal Diverticula Associated with “Refractory” Seropositive Rheumatoid Arthritis in Rural Kenya: A Case Report

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Abstract: Rheumatoid arthritis may be seropositive or seronegative. Seropositive rheumatoid arthritis is more common and usually presents with a more protracted course associated with multiple systemic involvement. Refractory cases of rheumatoid arthritis are commonly seen in seropositive rheumatoid arthritis, leading to significant morbidity. Effective management of this leads to the use of increasing doses and variety of disease-modifying anti-rheumatic drugs. In addition to the traditional risk factors for refractory disease, uncommon and unusual factors may be elicited. We present a case here in which an unusual surgical finding was responsible for apparently refractory disease.

Keywords: Seropositive rheumatoid arthritis, megaesophagus, esophageal diverticula, methotrexate, refractory rheumatoid arthritis, Kenya.

1. CASE SUMMARY

Presenting illness and physical examination

A 25-year-old single mother of one from Nakuru town, Kenya, was referred to us with a history of refractory seropositive rheumatoid arthritis (had not responded to methotrexate, hydroxychloroquine, prednisone, or azathioprine), with extra-articular manifestations (sicca symptoms with xerostomia and keratoconjunctivitis). Besides, she'd developed progressive dysphagia, postprandial emesis, and severe acid reflux symptoms with progressive weight loss over a period of 2-3 months prior to her presentation to us. The rheumatoid arthritis had been diagnosed 6 months prior when she presented with a 3-month history of symmetrical polyarthritis affecting both fingers and toes; and associated with polysynovitis (multiple tender swollen joints), early morning stiffness of the joints, and dry eyes and mouth (sicca symptoms). The serum rheumatoid factor had been positive, and she'd been started on increasing doses of various disease-modifying anti-rheumatic drugs (DMARDS) and steroids without much improvement. At her presentation to us, she was on Azathioprine 100mg daily

and Prednisone 20mg daily. Maximum possible doses of methotrexate and hydroxychloroquine had reportedly been tried unsuccessfully and hence stopped. She had been fully compliant with her medications, which were administered by her mother.

Clinically, she was in severe pain distress: febrile at 38°C, blood pressure 98/58 mmHg, pulse rate 121 bpm, saturating at 93% in room air, random blood sugar of 74 mg/dl, and only weighing 40kg. She had bilateral conjunctival injection (in keeping with the keratoconjunctivitis sicca), dry oral mucosa, and widespread dental caries (also a sicca manifestation). Her musculoskeletal exam elicited polyarthritis with polysynovitis involving both hands (metacarpophalangeal and proximal interphalangeal joints), both feet (metatarsophalangeal and proximal intertarsal joints), bilateral wrists and ankles, right elbow, and bilateral temporomandibular joints (she could only open her mouth 2cm wide). Her right thumb had a Z-deformity, and the left index finger had a swan-neck deformity. The range of motion across all joints as per the capsular pattern was severely limited by pain. She had moderate epigastric tenderness with no peritonism or organomegaly. Her chest had coarse bilateral crackles, worse on the right side. The rest of the exam was unremarkable.

Diagnostic workup

Her important and relevant initial etiological work-up included a complete blood count showing neutrophilic leukocytosis with a total white cell count of $22.3 \times 10^3/uL$, hemoglobin of 12g/dl, platelets of $721 \times 10^3/uL$, random blood glucose of 108mg/dl (normal), urinalysis showing uncountably many pus cells/hpf (consistent with urinary tract infection), negative pregnancy test, negative HIV test, negative malaria test, normal renal and liver function tests, positive rheumatoid factor, elevated ESR of 65mm/hr. A chest x-ray showed a widened mediastinum but no pneumonia. A subsequent contrasted CT scan chest showed gross dilatation of the esophagus, with the bulk lying in the right hemithorax and containing particulate matter and mottled gas. There was an associated large sliding/hiatus hernia at the gastro-esophageal junction with the cardia and portion of the body of the stomach being intra-thoracic. Upper gastrointestinal endoscopy showed a large esophageal diverticulum in the right hemithorax, markedly narrow and spastic esophago-gastric junction, with Hills’s grade IV hiatus hernia. Barium swallow showed flow of the barium to the right hemithorax, minimal entry to the stomach, and a bird’s beak appearance at the lower esophageal-gastric transition (see Figures 1 and 2 below of some of her initial x-ray images).



Figure 1: Barium swallow of the patient (PA view) showing markedly dilated esophagus/megaesophagus (black arrows) with contrast pooling in the right hemithorax and a distal bird’s beak appearance at distal esophagus

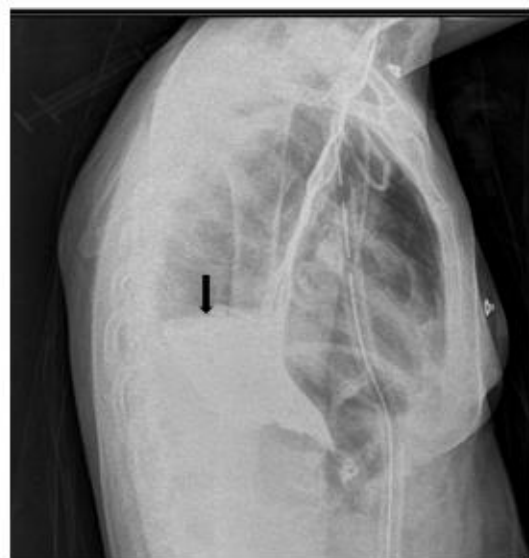


Figure 2: Barium swallow of the patient (Lateral view) showing megaesophagus with contrast pooling in the right hemithorax (black arrow) and a distal esophagus bird’s beak appearance.

Management and follow-up

Following initial successful resuscitation, an interval Heller myotomy was performed to allow her oral feeding and medications. Some of the particulate matter seen in the esophageal diverticulum was washed out endoscopically, with drug particles noted in the effluent. She was referred to cardiothoracic surgery but only got to be reviewed 1 year later due to financial constraints and the COVID-19 global pandemic. She subsequently underwent a trans-hiatal esophagectomy with gastric conduit, a Heineke-Miculicz pyloroplasty, and the placement of a feeding jejunostomy tube. Intraoperatively, she was found to have a massive mega-esophagus with impacted old feeds and medications and a large hiatus hernia with the gastric cardia in the lower chest. She had an uneventful postoperative recovery and follow-up. Due to the pre- and intra-operative findings, it was concluded that the rheumatoid arthritis had not been responding to initial treatments simply because most of the medications were not physically reaching her stomach; instead getting impacted in an ever-increasingly solidifying particulate matrix. With surgical restoration of gut continuity and integrity, she was successfully switched to only methotrexate, starting @10mg/week with folic acid (folate) supplement @ 5mg/day (this being the cheapest and most widely available DMARD). She had low-moderate flare-ups (as determined by Disease Activity Score-28) in subsequent follow-up clinic visits, with appropriate adjustments of her doses and judicious use of analgesics and short courses of low-dose oral prednisone. It's now been over two years since this definitive surgical intervention. She steadily gained weight due to better feeding to a peak of 72kg (from a nadir weight of 38kg in the first 2 weeks post-esophagectomy). Her rheumatoid arthritis became so well controlled that her methotrexate dose was tapered down to 5mg/week (from a peak dose of 20mg/week). Six months ago, she got married, and expressed a desire to conceive. The methotrexate was stopped shortly after that, while the folate continued without any further flare-ups. She's currently pregnant, with ongoing multidisciplinary monitoring.

2. DISCUSSION

Rheumatoid arthritis (RA) may be seropositive (positive rheumatoid factor or anti-cyclic citrullinated peptide antibody) in up to 80% of cases, or seronegative (negative rheumatoid factor and anti-cyclic citrullinated peptide antibody) in the remaining cases [1]. Patients with seropositive rheumatoid arthritis comparatively tend to have a more protracted course of disease with significant extra-articular manifestations [2], including involvement of lacrimal and salivary glands (causing the sicca symptoms), skin (e.g., erythema nodosum), lungs (e.g., pulmonary nodules, interstitial lung disease), cardiac (e.g., accelerated atherosclerotic coronary disease) [2, 3]. Gastrointestinal manifestations may be due to the RA itself, its treatment (especially steroids and non-steroidal anti-inflammatory drugs [NSAIDs]), or other concomitant autoimmune diseases. This may involve small and large bowel inflammatory ulcerations, strictures, diverticular complications, perforations, Felty's syndrome, vasculitis, and amyloidosis, among others [4]. Oropharyngeal-esophageal involvement with dysphagia is typically seen in RA with temporomandibular joint involvement. Specific esophageal manifestations of RA may range from functional myopathic or neuropathic esophageal dysmotility to esophageal mucosal damage from repeated acid reflux or opportunistic infections [5]. The latter may result in progressive megaesophagus or esophageal diverticula.

We believe that our patient developed the megaesophagus and the diverticula due to the RA itself and possibly also from its initial therapy with steroids and NSAIDs, which caused a hyper-acidic milieu. The large hiatus hernia (most likely due to the RA itself, and the megaesophagus) also led to severe gastroesophageal reflux of acid, which maintained and propagated the esophageal dysfunction. Previously swallowed medications, including DMARDS and steroids, were repeatedly refluxed into an ever-solidifying particulate matrix in the esophageal diverticula. This led to non-therapeutic plasma drug levels, leading to poor control of the RA activity despite up-titration of the doses and the addition or replacement of various DMARDS and steroids. At all times since diagnosis, she'd been adherent to her medication. When the surgical causes of the apparently refractory RA were corrected, the disease itself was subsequently easily controlled with a single, cheap, and easily available DMARDS, i.e., methotrexate. Methotrexate is the usual first choice for DMARDS in the management of RA. Methotrexate may be used as monotherapy or in combination with other agents and is given in a weekly dose titrated to clinical response. This practice is endorsed by the American College of Rheumatology in its 2021 guidelines [6]. Folic acid is given concurrently to prevent folate-deficiency anemia that may arise from methotrexate-induced dihydrofolate reductase inhibition. Methotrexate is contraindicated during pregnancy and lactation. Interestingly, RA as well as several other rheumatologic diseases tend to go into remission during pregnancy [7]. This is why our patient was successfully weaned off methotrexate, and has not had any flare-ups while pregnant. Alternative conventional DMARDS, e.g., hydroxychloroquine, sulfasalazine, leflunamide, and azathioprine, may be used as second- or third-line therapies in RA according to various clinical society and institutional guidelines.

3. CONCLUSION

Patients with seropositive rheumatoid arthritis may have multiple systemic involvements, a protracted course of illness, and refractory disease. Poor drug compliance is the most common cause of refractory disease. However, clinicians should carefully evaluate patients with refractory disease for unusual causes, including surgical ones (e.g., megaesophagus and esophageal diverticula), which may sequester orally administered drugs. Such a mechanical process eventually prevents effective plasma drug concentrations. Luckily, they're amenable to definitive surgical correction. Admittedly, more work needs to be done to fully and unequivocally elucidate the pathogenesis of such surgical findings in the natural history of rheumatoid arthritis.

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