Aerospace Medicine Clinic

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You are the flight surgeon attached to a U.S. Air Force (USAF) flying squadron. A healthy and experienced 36-yr-old male aviator presents to the Flight Medicine clinic with a few months of atraumatic bilateral shoulder and hip pain that awakens him from sleep. He also reports recurrent night sweats a few times a week and daily fatigue. His joint pain is worse at night and in the morning, however, it improves after about 1 h with movement and over-the-counter ibuprofen. He denies past medical history, surgeries, or use of other medications or supplements. He also denies previous joint injuries, bug bites, recent travel or deployments, rash, weight change, easy bleeding or bruising, personal or family history of malignancy or rheumatic diseases, cold intolerance, depression, or sleep problems. He is not actively flying and is uncertain if his symptoms would interfere with flight duties. His physical examination and vitals are unremarkable, with no joint swelling, palpable thyroid, pallor, rash, or lymphadenopathy. Laboratory screening for bony and hematologic malignancy, chronic infection, fatigue, and inflammatory/rheumatic etiologies (e.g., erythrocyte sedimentation rate/C-reactive protein, rheumatoid factor, anticyclic citrullinated peptide, antinuclear antibody, creatine kinase) is normal. Hip/shoulder X-rays are normal, and magnetic resonance imaging shows mild joint effusions in both shoulders and the left knee, with no masses or lesions. His symptoms are initially controlled with naproxen (500 mg) twice daily; however, his symptoms progress, and he develops joint swelling in his hands and feet. Rheumatology consultation is obtained. His 2010 American College of Rheumatology-European League Against Rheumatism classification criteria score was 6 due to diffuse joint involvement and duration of symptoms, so he was diagnosed with seronegative rheumatoid arthritis (RA).[1] The aviator's RA flare is initially managed with oral prednisone and a combination of disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX) with folate and hydroxychloroquine (HCQ), which led to a significant improvement in symptoms.

1. This pilot is seeking a return to flying status after achieving remission of RA. He is asymptomatic with no headaches, neck pain, upper extremity paresthesias or weakness, vertigo, or tinnitus. He has a normal musculoskeletal and neurological exam. Which studies should be obtained prior to recommending return to flying status for this pilot?
   A. Complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate/C-reactive protein.
   B. Cervical spine X-rays with flexion and extension, anteroposterior, lateral, and odontoid views.
   C. Morning cortisol and adrenocorticotropic hormone stimulation test.
   D. Chest X-ray, pulmonary function test.

ANSWER/DISCUSSION

1. B. RA is a chronic autoimmune disease affecting ~0.5% of U.S. adults and is characterized by synovial inflammation leading to progressive joint destruction, with the potential for severe articular and extra-articular manifestations of aeromedical concern.[1] DMARDs, such as MTX, HCQ, tumor necrosis factor inhibitor biologics, and glucocorticoid adjuncts, can have significant side effects of aeromedical concern such as pneumonitis, retinopathy, cytopenias, hypersensitivity reactions, and neuropsychiatric events, as well as new and reactivated infections. One complication is cervical-spine disease, which affects up to 86% of RA patients and includes disease etiologies such as atlantoaxial instability (AAI) or subluxation (AAS) due to synovial inflammation in the atlantoaxial joint, facet joints, and spinal ligaments.[10] Direct repetitive trauma through hyperflexion or hyperextension, such as during a high-G maneuver or ejection, may cause severe neurological impairment or death due to brain stem, spinal cord, and vertebral artery compression and injury.[10] The USAF restricts aviators with RA to non-ejection-seat aircraft to reduce the likelihood of such catastrophic complications.[8] Aviators with RA should be screened for cervical spine disease with cervical spine X-rays, including anteroposterior, lateral, odontoid, and flexion-extension views, every 2–3 yr

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as ~50% of RA patients with radiographic instability are asymptomatic.[1,10] Early treatment with novel DMARDs can prevent long-term progression, disability, and comorbidities.[10] If aviators become symptomatic, they should be brought off flying status and referred for magnetic resonance imaging of the cervical spine with dynamic flexion-extension and neurosurgery evaluation.[10]

2. Since this USAF pilot with RA is being treated with maintenance HCQ, which annual test should be obtained while being treated with this medication?
   A. Retinal exam by optometrist or ophthalmologist.
   B. Complete blood count.
   C. Liver function tests.
   D. Electrocardiogram for QT evaluation.

ANSWER/DISCUSSION

2. A. HCQ retinopathy is a "bulls-eye" maculopathy with central, extensive parafoveal retinal pigmented epithelium loss associated with severe and irreversible vision loss.[9,11] Clinical symptoms of aeromedical concern include: dropout of letters from words when reading; photophobia; blurred distance vision; reduced night vision; visual field defects ("parafoveal scotomata"); and flashing lights.[9] The exact mechanism of HCQ toxicity to retinal foveal photoreceptors and retinal pigmented epithelium is unknown.[11] The disease is highly prevalent, affecting ~7.5% of patients after 5 yr and ~20–50% after 20 yr.[11] Incidence is higher with specific risk factors per the American Academy of Ophthalmology 2016 guidelines, such as high dosage (>5 mg · kg^{-1} actual body weight) (odds ratio = 5.67), renal impairment (given that HCQ is renally excreted) (odds ratio = 2.06), and preexisting macular disease.[11] Screening is important as the disease is common and structural changes that may precede symptoms are detectable on common objective tests, such as spectral domain optical coherence tomography. Early detection of retinopathy and cessation of HCQ can potentially stop progression and yield visual improvements. However, effects are usually irreversible, as structural defects on spectral domain optical coherence tomography persist and—due to the long half-life of HCQ—may even progress for months to years.[11] It should also be noted that screening guidelines vary by organization.[11]

3. Since this aviator is being treated with MTX, which treatment would NOT lower his risk for MTX-associated pneumonitis (M-pneu)?
   A. Daily vitamin C.
   B. Calcium/vitamin D supplementation.
   C. Folic acid.
   D. Daily acetaminophen.

ANSWER/DISCUSSION

3. C. MTX is a common first-line DMARD in both the United States and Europe.[1,5] One severe side effect of aeromedical concern seen with this medication is M-pneu, a subacute hypersensitivity reaction and drug toxicity in alveolar cells to MTX that affects ~0.3–12% of patients with RA, usually within 1 yr of starting MTX.[6,7] Many common side effects of the medication, such as gastrointestinal, hepatic, and bone marrow toxicity, are more common with high doses prescribed for oncologic indications, not rheumatologic dosages. Typical dosing for RA is between 15–25 mg · wk^{-1}, and most side effects can be prevented with daily folic acid supplementation. However, M-pneu is not preventable with folate supplementation.[7] Patients typically present with nonspecific pulmonary symptoms such as cough, dyspnea, and fevers, and lab work may demonstrate eosinophilia.[6] Chest X-ray shows a nonspecific interstitial pneumonia-type presentation, and chest computed tomography may show ground-glass opacities followed by fibrosis, which may explain restrictive pulmonary function tests commonly found in patients with M-pneu.[6] M-pneu is a diagnosis of exclusion. More likely diagnoses that should be ruled out are viral pneumonia, including SARS-CoV2, other atypical pneumonia etiologies, and RA-interstitial lung disease—although the latter typically has a more chronic course.[6] Flight risks include: worsening of hypoxia at altitude; G-intolerance; acceleration atelectasis; and even incapacitation or death. An ~13–30% death rate has been reported per multiple small retrospective cohorts with potentially higher risk if M-pneu occurs within 6 mo of initiating MTX.[6,7] Given the potentially severe outcomes of M-pneu, MTX should be stopped and patients evaluated in the emergency department to consider admission for immunosuppression with steroids, and rarely cyclophosphamide or tocilizumab.[6,7] Most patients fully recover, although recurrence with MTX treatment is common.[6]

4. Which common adjunct medication used with DMARDs during RA flares that this patient was treated with may be associated with neuropsychiatric events such as depression, delirium, mania, and psychosis?
   A. Folic acid.
   B. Prednisone.
   C. MTX.
   D. Adalimumab.

ANSWER/DISCUSSION

4. B. Oral glucocorticoids are commonly used as adjuncts to DMARDs to treat RA flares.[1,5] Although aviators are unlikely to fly during an active RA flare, it is important to be aware of medication complications from these commonly used drugs that may impair flight duties.[3] Besides potentially developing exogenous Cushing's syndrome or secondary adrenal insufficiency, long-term steroid usage can lead to neuropsychiatric events that are not conducive to flying duties, such as mood disorders, psychosis, and suicide.[3] In a large 2012 retrospective cohort in the United Kingdom, new oral glucocorticoid prescriptions among ~373,000 adults treated by primary care physicians led to a significantly increased risk of severe neuropsychiatric events relative to ~1.2 million nontreated

patients; a ~7-fold increased risk for suicide, 5-fold for delirium, 4-fold for mania, and 1.5-fold for panic disorder were observed in adjusted models.[3] The absolute risk was ~22 per 100 person-years, which is well above the 1% risk for severe annual events accepted by the aeromedical community.[3] However, these results may not be generalizable to active aviators, who are likely at decreased likelihood of developing neuropsychiatric events than this study population for a few reasons. First, aviators should not be flying with active RA or other diseases where steroids are indicated, such as pneumonia, asthma, chronic obstructive pulmonary disease, or temporal arteritis. Second, 24% of the exposed population had a history of mental illness, while aviators with a history of significant mental illness would likely be disqualified from flying duties. Also, aviators, especially military aviators, are younger than the study average of 57 yr old. Older age was associated with an increased likelihood of certain mood disorder events. Lastly, aviators with RA would be treated with lower dosages of prednisone than the average study participant, equaling $10\,mg \cdot d^{-1}$ per the American College of Rheumatology and up to $20\,mg \cdot d^{-1}$ per the Federal Aviation Administration (FAA). Lower dosage glucocorticoids had lower risk in the study, although some residual risk was seen in $11–20\,mg \cdot d^{-1}$ vs. $10\,mg \cdot d^{-1}$ or less for delirium and panic disorder (hazard ratio 1.85, 95% confidence interval 1.57–2.17 and hazard ratio 3.42, 95% confidence interval 1.53–7.67), respectively.[3] The highest rates of neuropsychiatric events occurred in individuals prescribed daily prednisone doses of 40 mg or higher. Nevertheless, this is a medication side effect worth remembering should an aviator with RA present with new mood symptoms to your clinic.

AEROMEDICAL DISPOSITION

Your pilot was taken off flying status due to the severity of his articular symptoms and RA diagnosis. He was ultimately granted a non-ejection-seat waiver to reduce atlantoaxial instability/subluxation complications during aviation operations with follow-up required in 1 yr. Waiver was recommended for a few reasons. He was in prolonged remission per Rheumatology for greater than 6 mo, with a Clinical Disease Activity Index score of 0 and no impairment in fine-motor functioning of hands or feet that would affect aviation duties. Also, he had successfully tapered off of MTX and prednisone with intact hypothalamic-pituitary-adrenal axis function and was doing well on HCQ without side effects or retinal disease. He requires annual rheumatology and optometry evaluations.

Aviators with RA are allowed to fly in the USAF with certain restrictions. They can be considered for a waiver if in disease remission per Rheumatology, with no extraarticular manifestations while taking aeromedically approved medications without adverse side effects.[8] As of 2022, the only aeromedically approved medications in the USAF are sulfasalazine, HCQ (with a normal dilated ocular exam), adalimumab, infliximab, and etanercept (U.S. Air Force. Official Air Force aerospace medicine approved medications, 2022 Sept. 21. Available to those with access.).[8] Aviators on non-aeromedically approved medications can be considered for waiver on a case-by-case basis. Also, systemic steroid usage is neither allowed for flying duties nor waiverable, and usage for more than 3 wk requires demonstration of an intact hypothalamic-pituitary-adrenal axis.[8] Aviators are restricted to non-ejection-seat aircraft due to the potential for catastrophic complications from atlantoaxial instability/subluxation.[8] From 2015–2022, 22 of 28 RA waivers were approved for USAF aviators.

The FAA also allows aviators with RA to fly if they meet Conditions AMEs (Aviation Medical Examiners) Can Issue criteria, which include stability per Rheumatology, mild to moderate symptoms without limitations, and disease limited to joint(s) with normal complete blood count and liver and renal function.[4] If they fail to meet these criteria, they are deferred to the FAA and may be considered for Special Issuance. The FAA allows ≤20 mg prednisone-equivalent daily, MTX, HCQ with normal eye exam, and six different biologics for aviators with variable required no-fly time after each use.[4] The U.S. Navy considers RA disqualifying.[2] The U.S. Army considers potential waivers for RA if the aviator is asymptomatic and treated with aeromedically acceptable medications (U.S. Army Aeromedical Activity. Systemic rheumatologic diseases. In: Aeromedical policy letters and aeromedical technical bulletins. 2021:211-212. Available to those with access.).

Rheumatoid arthritis is a common disease that may cause significant aeromedical concerns. Early diagnosis and treatment are critical for patient health and return to flight status. Frequent monitoring is necessary to detect disease progression and potential medication side effects.

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