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Ultrasonographic Evaluation of Splenic Enlargement in Athletes with Acute Infectious Mononucleosis.

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Abstract

Objective: To quantitatively assess the degree and rate of splenic enlargement and the time required for regression of splenic enlargement in collegiate athletes diagnosed with acute infectious mononucleosis (IM).

Design: Prospective Cohort study

Setting: Academic Medical Center(s) outpatient sports medicine clinic.

Study Participants: Volunteer Division I University athletes.

Interventions: A limited abdominal ultrasound was performed on each participant by a licensed and experienced ultrasonographer. Splenic measurements were taken to assess maximum splenic length. Athletes that were subsequently diagnosed with infectious mononucleosis (clinical illness and a positive Monospot) underwent serial splenic ultrasounds and physical exams (weekly) until resolution of clinical symptoms and splenic enlargement (as determined by ultrasound measurements).

Main Outcome Measures: Percent enlargement of spleen size (length) from baseline. Time (in days) from onset of clinical illness to maximum splenic length. Time (in days) required for resolution of splenic enlargement.

Results: Twenty subjects were diagnosed with acute IM during over a five-year time period. Maximum splenic length increased a mean of $33.6\% \pm 19.9\%$ from baseline values. Peak splenic enlargement was reached a mean of 12.3 ± 5.1 days from onset of clinical illness. A linear model demonstrated that spleen size decreases approximately 1% per day after reaching peak splenic enlargement.

Conclusions: The majority of athletes with IM experience a moderate degree of splenomegaly. Peak splenic enlargement occurred within two weeks from the time of symptom onset in most cases, but may extend to 3.5 weeks. The rate of splenic enlargement appears to be predictable for an individual who develops IM. Ultrasonographic data further show that splenomegaly associated with acute IM infection resolves within 4-6 weeks of symptom onset in the majority of cases.

Introduction:

Infectious Mononucleosis (IM), the common clinical syndrome caused by the Epstein-Barr virus, warrants particular attention in the setting of sport.

The decision to allow an individual recovering from IM to resume activity is primarily guided by the goal of limiting the risk of significant complications, mainly that of splenic rupture. While the incidence of splenic rupture in cases of IM is estimated to be small 5 (0.1—0.2%) [1], [2], the consequences can be fatal. The spleen is thought to be vulnerable to rupture in cases of IM secondary to enlargement below the usually protective rib cage. The spleen is also believed to have an increased fragility owing to architectural changes caused by lymphocytic infiltration.[3],[4] Because the majority of reported splenic ruptures occur during the first three weeks of illness, splenic vulnerability is theorized to peak during this timeframe.[1], [2]

Historically, physicians have relied on their clinical acumen and expert opinion to make return to activity decisions. Recent recommendations suggest that individuals restrict physical activity and competitive athletics for a period of 3- 4 weeks following onset of clinic symptoms.[5] Gradual return to activity is recommended following this convalescent period provided that the patient is asymptomatic.[5]

To date, no studies have prospectively evaluated the timing and degree of splenic enlargement in individuals with acute infectious mononucleosis. Therefore, we used ultrasonography to measure the degree and rate of splenic enlargement as well as the time required for regression of splenic enlargement in collegiate athletes diagnosed with acute IM.

Methods:

Prior to initiation, the study protocol was approved by each participating university's Institutional Review Board. Informed consent was obtained from each participant before commencement of data collection.

Volunteer athletes from three Division I NCAA Universities were recruited to participate in the study. Individuals were excluded if they were less than 18 years of age or had previously undergone a splenectomy. Each participant had demographic data collected at the time of the pre-participation physical examination, conducted prior to the commencement of athletic participation. This information included gender, measurement

of height and weight, and race. Subjects then underwent a review of their medical history and a physical examination as part of the routine pre-participation physical exam. This was then followed by a limited abdominal ultrasound to obtain baseline splenic measurements.

Ultrasonography (US) was performed by an experienced and licensed technician at each university medical center. The examination was performed using the ATL HDI 3500 or 5000 ultrasound machine and a curved 5.2 Megahertz (MHz) transducer. (Phillips Medical Systems Co., Bothel Washington). The spleen was visualized with the participant in a right lateral decubitus position. Measurements were then taken assessing the splenic length and width with the maximum dimension being recorded. Splenic length was used for all statistical analysis as it was previously found to be the most reliable measure.[6] Images from all participants were saved and stored on compact discs. These were forwarded to the PI for storage and for review by a single radiologist (VK) experienced in reading abdominal ultrasounds. The radiologist confirmed the splenic measurements and noted any significant additional findings. A single ultrasound exam was used to determine the participants' baseline spleen measurements.

For the purposes of this study, clinical illness (presence of at least one of the following symptoms: sore throat, exudative pharyngitis, fatigue, fever and cervical lymphadenopathy) and a positive monospot test were necessary for inclusion in the IM cohort. The onset of clinical symptoms of acute IM was determined by patient recall at the time of diagnosis. Those individual athletes subsequently diagnosed with IM underwent serial splenic ultrasounds and physical exams. Follow –up ultrasounds were performed weekly until splenic measurements returned to baseline, reached a plateau, or the patient was lost to follow up.

Data Reduction and Statistical Analysis:

Ultrasound data from subjects diagnosed with IM were converted to a percentage change score from baseline with the equation $(\text{current length} - \text{baseline length}) / \text{baseline length}$. This conversion normalized the variable spleen size for statistical comparison. The data were analyzed initially by subject, with individual regression analyses to evaluate the linearity of the relationship between the recovery of spleen size from peak enlargement and the number of days from onset of the symptoms. A mixed linear model with random intercept and slope was used to estimate the mean slope (the mean rate of percent change) of spleen size by days from the onset of symptoms. Additionally, the mean intercept, the mean percent change of spleen length at day 0 (onset of symptoms) was determined.

Results:

1822 subjects at three academic sports medicine centers enrolled in the study and had baseline US exam performed over a five year period. During this time twenty participating athletes were diagnosed with IM (See Table 1).

Table 1: Data for subjects (N=20, 12 Females, 8 Males) diagnosed with Acute Infectious Mononucleosis.

	Mean \pm S.D.	Range
Height (inches)	69.05 \pm 2.11	65-73
Weight (lbs.)	158.0 \pm 26.81	120-206
Baseline Spleen Length (cm)	10.56 \pm 1.45	7.57-12.58
Max. Spleen Length (cm)	14.02 \pm 2.0	10.7-18.6
Number of US (follow up)	3.45 \pm 1.47	1-6

The mean number of days from the onset of clinical symptoms until the first follow up ultrasound was 9.9 ± 4.5 days. (range 6-23 days). The subjects demonstrated no significant change in height or weight from baseline examination at the time of follow up.

The mean increase in maximum splenic length (N=20) was $33.6\% \pm 19.9\%$ (range 3.9% -95.8%) from baseline values. All twenty athletes with IM (100%) demonstrated an increase in splenic length. Eighteen of the twenty athletes had at least 2 ultrasounds following their diagnosis (Mean 3.45 ± 1.47). In 17 of these individuals, ultrasonography demonstrated a peak in spleen enlargement occurring within 23 days of symptom onset (Mean 12.3 ± 5.13 days). One case (#3000) was lost to follow up at day 16 of illness without reaching a peak splenic length. (See Figure 1)

Regression of Splenic Enlargement

A linear trend was very evident as the average R^2 for an individual in this population was $.88 \pm .15$ (N =18). Two of 20 subjects only had 1 data point post-baseline and therefore were not used in this calculation. (See Figure 2) The mixed linear model analysis revealed a significant relationship between percent change and time. The estimated mean slope representing the mean rate of recovery by day, is equal to -1.058 ($t = -9.178$, $p < 0.001$); the estimated mean intercept, representing mean percent change at day 0, is 41.45 ($t = 10.81$, $p < 0.001$). The estimated variances of slope and intercept are 0.015 and 174.90, respectively. The Wald test results reveal significance of the intercept variance ($p = 0.014$) indicating significant variability in percent change at day 0 among subjects, but the variance of slope is not significant, implying that variability of the rate of recovery

among subjects is not significant. The estimated linear model can be used to estimate recovery spleen size by days; percent change of spleen size = -1.058 (days from onset of symptoms) + 41.5.

Discussion:

Splenic enlargement associated with acute IM has historically been thought to occur with some variability. Prior estimates based solely on clinical exam likely underestimate the presence of an enlarged spleen. In a natural history study of individuals with EBV IM, Rea et al found that only 8% of affected individuals had palpable splenomegaly.[7] In contrast, Dommerby et al used serial ultrasonography to document splenomegaly in patients hospitalized with IM. Splenomegaly (exceeding 25%) was found in 100% of these cases, whereas no control cases exhibited greater than a 10% enlargement of spleen length. [8] Subjects in our study were healthy college athletes, all of whom were treated as outpatients. Nonetheless, we found a similar splenic response with all subjects demonstrating some degree of increased splenic size (range 3.9% - 95.8%) and a mean increase of 33.6%.

Because the majority of reported splenic ruptures occur within the first three weeks of clinical illness [1], it can be speculated that the rapid progression and peaking of splenomegaly occurring within this period plays a role in rupture. To our knowledge, information regarding the initial rate of splenic enlargement in cases of IM has yet to be reported. By obtaining baseline spleen measurements on our subjects we were able to prospectively follow those individuals that contracted acute IM. In our subject cohort, a rapid rise in spleen length early on in the course of illness was clearly demonstrated. On average, the spleen reached its maximum dimension 12.3 days from onset of clinical symptoms. This finding lends support to the notion that the spleen is at greatest risk of rupture early in the clinical course of IM.

The presence of splenomegaly has traditionally been a reason to limit physical activity in those with IM. Being able to quantitate the time frame for resolution of splenomegaly is therefore likely to be regarded as useful information. Physical examination is unfortunately not a reliable way to determine the presence or absence of an enlarged spleen.[9] Using a standard “cutoff” to define splenomegaly via ultrasonography is also potentially flawed since it has been recently shown that there is a wide variability of normal splenic dimensions.[6] Regression of splenomegaly associated with IM has been previously documented via serial ultrasonography.[8] Cases in this study; however, had no baseline splenic measurements prior to their illness. As a result, the degree of splenic enlargement and the time needed for an individual to return to “normal size” may be either under-estimated or over-estimated.

Our data suggest that it is possible to predict the relative percent change of spleen length on a given day of illness, knowing the onset day of clinical symptoms. (Percent change of spleen size = -1.058 (days from onset of symptoms) + 41.5). Given this model, it is possible to conclude that while the actual splenic measurements may vary significantly among individuals with IM, the rate of splenic regression is fairly predictable.

Limitations to this study deserve specific mention. Working with a small, select group of collegiate athletes raises a question regarding the generalizability of our findings to other patient populations. This cohort was specifically targeted because of the relatively high incidence of IM in college-aged individuals and the return to play issues that arise specific to this population. Student athlete schedules did pose some problems in assuring follow up of subjects as noted by the loss of two subjects after a single post baseline ultrasound exam. The inclusion of additional ultrasonographic data points from these two subjects could have altered the reported time to peak splenic length, the maximum percentage change in spleen size, and our linear prediction model.

The specific date of symptom onset is inherently affected by recall bias. Additionally, there was a wide range of time elapsed from symptom onset to diagnosis (and as a result first follow up ultrasound) Therefore, the time to peak splenic length and also the maximum percentage change in spleen size could be affected. Because the overwhelming majority of subjects' maximum spleen length was seen at the initial post baseline US, it is likely that the data reported may under-estimate these averages.

Our data should be interpreted cautiously with respect to making return to physical activity decisions for athletic individuals. While we note that spleen enlargement consistently peaks by 3.5 weeks after onset of symptoms, this is not a clear indication that the spleen is safe from potential injury. It is important to note that no cases of splenic rupture occurred in our population. Thus, direct correlation between splenic size and risk of rupture as well as the relative risk of splenic injury at various stages of recovery in those with IM is still unknown and remains speculative. A study designed to answer these questions would require large numbers and likely be deemed unethical.

Conclusions

Individuals with acute IM routinely develop splenic enlargement during the course of their illness as demonstrated by serial ultrasonography. Spleen size increases most rapidly in the initial phases of illness, reaching its maximum in the first few weeks of clinical illness. Specific splenic dimensions vary significantly between patients, both when healthy (baseline) and when afflicted with IM. In contrast, once peak splenic length is reached, resolution of splenomegaly in individuals with IM follows a predictable linear pattern.

Given these findings, the use of US, for confirming the presence splenomegaly, is not recommended in managing patients with IM. Obtaining baseline studies for the millions of people at risk for contacting IM is not practical or cost effective. Further, without baseline measurements, the ability to assess the degree or presence of relative splenic enlargement is significantly limited.

Addendum:

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Figure Legends:

Figure 1: Graphic illustration of splenic length (ultrasonographic measurement) versus time from symptom onset in twenty subjects diagnosed with acute infectious mononucleosis. (Day 0 reflects baseline splenic length measurement).

Figure 2: Graphic illustration of 11 individual rates of change from subjects with more than 4 ultrasonographic measurements. The high level of R^2 illustrate the linearity of recovery while demonstrating the individual variability between subjects. The large black circles represent the average estimated regression for the entire cohort.

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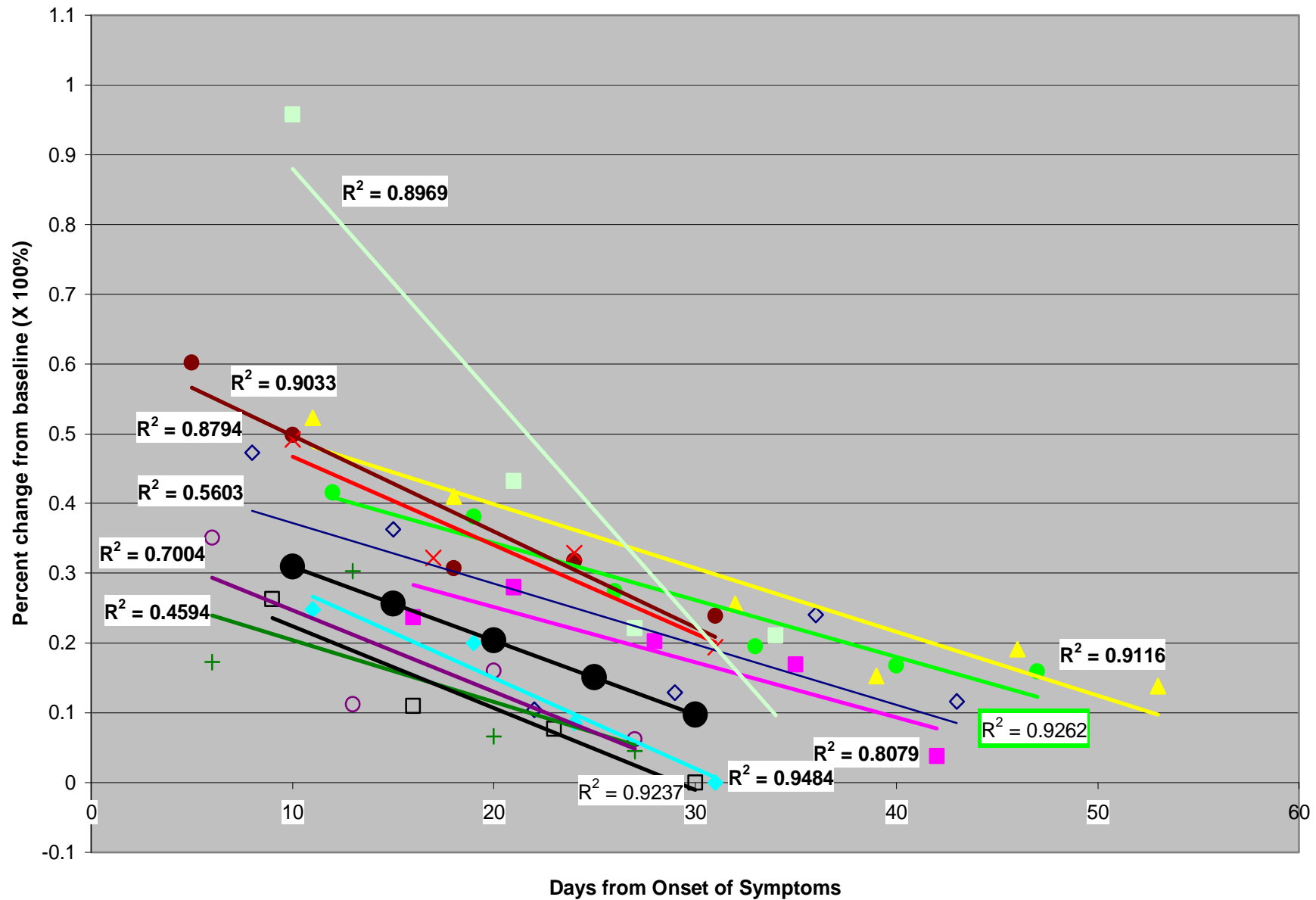


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