Quality of randomized clinical trials in juvenile idiopathic arthritis


Objectives. We evaluated the quality of randomized clinical trials (RCTs) of therapy for juvenile idiopathic arthritis (JIA) using an individual component approach and assessed temporal changes.

Methods. A systematic review of the literature was performed to identify all RCTs involving exclusively JIA patients. Two investigators independently assessed the identified articles for six quality indicators: generation of allocation sequence, allocation concealment, masking, intention-to-treat (ITT) analysis, dropout rates and clearly stated primary outcome.

Results. Fifty-two RCTs involving JIA patients were assessed. Generation of allocation sequence was unclear in 79% of the studies. Reporting of allocation concealment was adequate in only one-third of the studies. Masking was adequate in 73%, inadequate in 19% and unclear in 8% of the reports. ITT analysis was employed in 37% of the reports. Per-protocol analysis was used in 40% and in 23% the method was unclear. Most of the reports (67%) had dropout rates ≥20%. About half of the reports (n = 25) failed to show a significant effect of the experimental treatment. No significant associations were found between the study results and quality indicators. With the exception of adequate masking and dropout rate, all quality indicators showed a trend of improvement over the decades.

Conclusions. The quality of RCTs in JIA based on the selected indicators was poor. Although there were some positive changes over time, the reporting and methodological quality of trials should be improved. New, more powerful and acceptable RCT designs should be developed in this patient population.

Key words: Juvenile idiopathic arthritis, Randomized clinical trials, Systematic review, Quality.
randomized controlled trial; controlled clinical trial; multicentre study; clinical trial; English; and human studies. The terms were adjusted according to database-specific terms.

Data extraction

We selected the following quality indicators to reflect areas where bias (selection bias, performance bias, measurement bias and attrition bias) may occur in RCTs [12]. A data collection form was developed based on the selected quality indicator components as recommended by Khan et al. [12] The form was pilot-tested in three RCTs involving patients who did not have JIA. Two independent reviewers (L.A. and S.R.J.) used the form to extract data from the selected JIA articles. Disagreements were solved by consensus and consulting the other authors (J.B., P.S.S. and B.M.F.).

We extracted the following data from the trials: first author's name, publication year, study design (parallel, cross-over), number of study arms, compared interventions, total sample size, mean age of patients, study duration (in weeks), allocation concealment (adequate, inadequate, unclear), generation of allocation sequence (adequate, inadequate, unclear), masking (adequate, inadequate, unclear, not applicable), intent-to-treat (ITT) analysis (full or modified ITT, per-protocol analysis, treatment-received analysis, unclear), dropout rate (exact rate; no dropout, ≤20%, >20%), methods used to handle missing data, clearly stated primary outcome(s) (yes, no), type of primary outcome(s) (single, composite, multiple) and description, participating centres (single, multicentre or multinational) and the final conclusion of the study. We also evaluated the study funding source (not sponsored by industry, industry sponsored, not reported). The study was considered as industry sponsored if the pharmaceutical manufacturer was acknowledged by the authors or if any of the authors was affiliated with a pharmaceutical company. The main quality indicators of interest were allocation concealment, generation of allocation sequence, masking, intention-to-treat (ITT) analysis, dropout rate and clearly stated primary outcome (Table 1). The definitions for the indicators were selected based on the Consolidated Standards of the Reporting of Trials (CONSORT) guideline and previous studies [13–15].

Data analysis

Descriptive statistical analyses were performed using mean, s.d. or median for continuous data and frequencies and percentages for categorical data. Continuous data were compared using t-test and analysis of variance; categorical data were compared using chi-square test or Fisher’s exact test as appropriate. Two-tailed P-values were reported. Characteristics of the studies and quality indicators were described and the final results of the studies were compared with the quality items and funding source. Finally, we evaluated the change of quality indicators over time in decades defined by year of publication. SPSS 11.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used for data entry and analysis.

Results

Search results

After removing the duplicates, the applied search strategy identified 471 abstracts in total. The abstracts presenting non-randomized, cross-sectional comparative or cohort clinical studies were excluded (n = 417). Fifty-four full-text articles underwent full review. One study was excluded because it was not a truly randomized trial [16]. Another excluded study described only the pharmacokinetics of the drug [17]. The final review included 52 articles (Supplementary Appendix). Figure 1 presents the selection process of articles for the final review.

General description of studies

Table 2 presents general characteristics of the reviewed studies. There were eight cross-over studies. The remaining 44 RCTs used a parallel-group study design. Among them two studies

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TABLE 1. Quality indicators and definitions

<table>
<thead>
<tr>
<th>Item</th>
<th>Scale and definition</th>
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<tbody>
<tr>
<td>Allocation concealment</td>
<td>Centralized or pharmacy-controlled randomization, numbered or coded identical containers administered serially, on-site computer that gave allocation only after participant’s characteristics were entered, serially numbered opaque, sealed envelopes.</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Allocation was done by open, inadequate methods such as alternation of study identification numbers, date of visits or by date of birth, open allocation schedule, unsealed or non-opaque envelopes.</td>
</tr>
<tr>
<td>Unclear</td>
<td>Method was not specified.</td>
</tr>
<tr>
<td>Generation of allocation sequence</td>
<td>Adequate Sequence was generated by random tables, computer generation, coin-tossing or shuffling.</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Other methods such as case record number, date of birth, date of visit.</td>
</tr>
<tr>
<td>Unclear</td>
<td>Method was not specified.</td>
</tr>
<tr>
<td>Masking</td>
<td>Adequate Defined as double-masked by the authors, or when both patients and assessors were masked, or when assessors were masked in the studies where it was considered impossible to mask patients.</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Either patients or assessors were not masked in studies where it was feasible.</td>
</tr>
<tr>
<td>Unclear</td>
<td>Method was not specified.</td>
</tr>
<tr>
<td>ITT analysis</td>
<td>Full ITT All randomized patients were included in the analysis and kept in their original groups decided by randomization (regardless of any protocol violations, compliance and withdrawals).</td>
</tr>
<tr>
<td>Modified ITT Analysis included participants with baseline measurement and at least one follow-up evaluation, regardless of the time between baseline and the second measurement, or analysis excluded patients who were defined as ineligible after randomization or who never received the treatment.</td>
<td></td>
</tr>
<tr>
<td>Per-protocol Analysis included only patients who complied with the study protocol including exposure to treatment, availability of the outcome measurement and absence of major protocol violations (case-complete).</td>
<td></td>
</tr>
<tr>
<td>Treatment-received Analyses were done according to the treatment patients actually received, not according to their randomization groups or per protocol.</td>
<td></td>
</tr>
<tr>
<td>Clearly stated primary outcome</td>
<td>Yes If the primary outcome(s) was clearly stated.</td>
</tr>
<tr>
<td>No</td>
<td>If there was no clear specification about the primary outcome.</td>
</tr>
</tbody>
</table>
inconsistent reporting in some studies. The range of the reported RCTs was impossible to evaluate because of the poor and quite similar to the results from all studies.

general characteristics of RCTs of medical treatment of JIA were RCTs in medication treatment of JIA (n = 36). The median sample size was 30 for cross-over RCTs (n = 8) and 49 for parallel RCTs (n = 44). The median sample size of parallel RCTs in medication treatment of JIA (n = 30) was 71. Other general characteristics of RCTs of medical treatment of JIA were quite similar to the results from all studies.

The overall mean or median age of patients in the included RCTs was impossible to evaluate because of the poor and inconsistent reporting in some studies. The range of the reported means was from 5.5 to 15.9 yrs if excluding one study reporting all patients being 25 yrs old.

Quality indicators
The generation of the allocation sequence and presence/absence of allocation concealment were unclear in the majority of RCTs (Table 3).

There were 35 double-masked studies. In seven studies, it was reportedly impossible to mask patients from the interventions (such as massage therapy, orthotic devices and dietary interventions). For such studies, we considered that masking was adequate if the outcome assessors were masked (n = 3).

ITT analysis was employed in 19 studies (37%); full ITT in 12 studies and modified ITT in 7. Twenty-one (40%) studies conducted per-protocol analysis, while in 12 studies (23%) the approach was unclear. Eighteen RCTs (32.7%) had dropout rates of more than 20% of the original sample while six studies (12%) had no dropout. Overall, the mean dropout rate was 15% (S.D. = 13; range from 0% to 52%). In two studies, it was impossible to estimate the exact dropout rate because of the inconsistent number of patients for different measured outcomes. No significant correlation was found between the indicators of study duration and exact dropout rate (Pearson’s correlation coefficient was 0.273; P > 0.05). Among 19 studies that used ITT, only five mentioned the method of handling missing data.

Only half of the reports clearly specified the primary outcome (n = 26). Among the 26 studies with clearly stated outcomes, a single primary outcome was evaluated in 16 cases and multiple outcomes in 10 of them. Multiple outcomes mostly included general clinical, articular and/or laboratory assessments. Overall, 16 studies (31%) measured at least one composite outcome out of the evaluated six; which 13 were clearly stated primary outcomes.

About 70% of all RCTs achieved an adequate rating in a maximum of three quality indicators out of the evaluated six; similar results of achieved numbers of quality indicators were observed for RCTs when we considered only medication treatment (Fig. 2).

**Quality indicators and study results**

In 25 (48%) studies, no statistically significant difference was found between the experimental and control treatments. The experimental treatment was superior in 25 RCTs. In one non-inferiority trial, the experimental treatment was found to be not inferior to standard treatment. In another study, the experimental intervention had less efficacy compared with the

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**Table 2. General characteristics of RCTs**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All studies (n = 52)</th>
<th>Medication treatment of JIA (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td></td>
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</tr>
<tr>
<td>Parallel RCTs, n (%)</td>
<td>44 (84.6)</td>
<td>30 (83.3)</td>
</tr>
<tr>
<td>Cross-over RCTs, n (%)</td>
<td>8 (15.4)</td>
<td>6 (16.7)</td>
</tr>
<tr>
<td>Control treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard, n (%)</td>
<td>30 (57.7)</td>
<td>21 (58.3)</td>
</tr>
<tr>
<td>Placebo, n (%)</td>
<td>22 (42.3)</td>
<td>15 (41.7)</td>
</tr>
<tr>
<td>Number of arms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two arms, n (%)</td>
<td>44 (84.6)</td>
<td>29 (80.6)</td>
</tr>
<tr>
<td>Three arms, n (%)</td>
<td>8 (15.4)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Involved centres</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single, n (%)</td>
<td>27 (51.9)</td>
<td>19 (52.8)</td>
</tr>
<tr>
<td>Multicentre, n (%)</td>
<td>14 (26.9)</td>
<td>6 (16.7)</td>
</tr>
<tr>
<td>Multinational, n (%)</td>
<td>11 (21.2)</td>
<td>11 (30.5)</td>
</tr>
<tr>
<td>Funding source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industry sponsored, n (%)</td>
<td>23 (44.2)</td>
<td>19 (52.8)</td>
</tr>
<tr>
<td>Not industry sponsored, n (%)</td>
<td>13 (25.0)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Source not reported, n (%)</td>
<td>9 (17.3)</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Unclear, n (%)</td>
<td>7 (13.5)</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>Median sample size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parallel RCTs, median (IQR)</td>
<td>49 (29–80)</td>
<td>71 (31–99)</td>
</tr>
<tr>
<td>Cross-over RCTs, median (IQR)</td>
<td>30 (22–39)</td>
<td>30 (29–47)</td>
</tr>
<tr>
<td>Median follow-up duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parallel RCTs, weeks (IQR)</td>
<td>24 (12–38)</td>
<td>24 (12–24)</td>
</tr>
<tr>
<td>Cross-over RCTs, weeks (IQR)</td>
<td>14.5 (8–28)</td>
<td>12 (8–16)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

**Table 3. Generation of allocation sequence, allocation concealment and masking**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All RCTs</th>
<th>Medication Trtm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generation of allocation sequence, n (%)</td>
<td>Adequate</td>
<td>11 (21.2)</td>
</tr>
<tr>
<td>Allocation concealment, n (%)</td>
<td>Inadequate</td>
<td>–</td>
</tr>
<tr>
<td>Masking, n (%)</td>
<td>Unclear</td>
<td>41 (78.8)</td>
</tr>
</tbody>
</table>

Fig. 2. Quality ranking of RCTs in JIA.
Clearly stated primary significant changes in reporting are likely due to the publication of
varies from 1% to 52% and from 2% to 39%, respectively [18].

diseases, the proportion of RCTs with reported adequate
generation, it had a 5-fold increase after 1995. In different
concealment was low; however, in contrast to random number
the three time periods. The overall reporting of allocation
population. We identified that most of the quality components
1977 to present; a number much lower than might be expected
and trial results are appropriately translated into clinical practice.

Adequate allocation concealment (%) 37 9 12 67\(^d\)

Dropout rate ≤ 20% (%) 67 55 71 67

Clearly stated primary outcome (%) 50 36 23 75\(^d\)

Temporal trends of the quality indicators

In order to show the temporal trends, RCTs were grouped in 10-yr
intervals by their year of publication. The first two RCTs in JIA
patients were conducted in 1977. The time periods and respective
number of RCTs were: 1976–85 (n = 11), 1986–95 (n = 17) and
1996–2006 (n = 24). Compared with the first decade, the number
of RCTs had almost doubled during the time period between 1996
and 2006. Table 4 shows the changes of quality indicators over the
decades.

With the exception of adequate masking and dropout rate,
all quality indicators showed a trend for improvement over the
decades. Compared with the second decade, the number of RCTs
reporting adequate allocation concealment increased almost
5-fold, and the number of RCTs with clearly stated primary
outcomes increased almost two times during the third decade.
Temporal increases in ITT analysis between the first and third
decades, and second and third decades were also statistically
significant.

Discussion

Rare disease trials face a number of methodological challenges in the
hope of determining the efficacy of an intervention. Thus, assurance of methodological quality is a critical and necessary
endeavour to ensure that limited resources are effectively utilized and trial results are appropriately translated into clinical practice.

Our study evaluated 52 RCTs for JIA patients beginning from 1977 to present; a number much lower than might be expected
when compared with more common diseases in the adult population. We identified that most of the quality components
that we evaluated were seldom met adequately.

The generation of random number sequences was the most
rarely reported quality indicator; this was mostly persistent across the three time periods. The overall reporting of allocation
concealment was low; however, in contrast to random number
generation, it had a 5-fold increase after 1995. In different
diseases, the proportion of RCTs with reported adequate randomization methods and adequate allocation concealment varies from 1% to 52% and from 2% to 39%, respectively [18].

While the overall rates of these quality indicators have been low,
significant changes in reporting are likely due to the publication of
the CONSORT statement in 1996 [13]. A study that compared the quality of RCTs in adult rheumatology between two time periods, 1987–88 and 1997–98, suggested that among the studied quality indicators only the reporting of allocation concealment increased significantly [19]. The improvement of quality over time could also be explained by the establishment of international networks such as the Pediatric Rheumatology Collaborative Study Group (PRCSG) in 1973 and the Pediatric Rheumatology International Trials Organization (PRINTO) in 1996, which aim to conduct high-quality clinical trials in children with rheumatic diseases.

Although the effect of adequate masking on the study’s main
results is still controversial [18], masking is still one of the current
standards for RCTs. Adequate masking should be guaranteed especially when the outcomes are susceptible to measurement bias.

In JIA, masking is especially important considering the use of
subjective outcomes such as patient or physician global assessments using visual analogue scales. In our study, double masking was used in 67.3% of the studies, and no positive temporal change was observed. This result is inconsistent with some other similar studies in the field. A study that assessed RCTs of rheumatological disorders in adults identified a higher rate of double masking of studies both between 1987 and 1988 (73.7%) and between 1997 and 1998 (85.5%) [19]. In contrast, in systemic lupus erythematosus only 54.3% of RCTs were double-masked [20]. The rate of double-masked studies might depend on the type of compared interventions. If we remove those studies in which double masking was thought to be unfeasible (n = 7), our number of RCTs with double masking rises to 77.8%.

The importance of clearly stated primary outcomes is very high in JIA and other systemic diseases, where outcomes are often subjective, and mortality is not a large concern. Depending on the evaluated treatment, the outcomes of interest can vary from study to study. In JIA, a validated measure of response to treatment was developed in 1997 [21]. The ACR Pediatric 30 score is a composite outcome consisting of six different measures, and is currently the most widely accepted method to estimate the response to treatment for JIA. Most probably, two factors, the publication of the CONSORT guideline and the development of a universal validated outcome, played a role in the significant increase in the number of RCTs in JIA with clearly stated outcomes. In the review of RCTs in systemic lupus erythematosus, adequately reported outcome was the only quality indicator that showed a significant improvement over time [20].

Although in this study the most frequently used approach was
per-protocol analysis, a significant temporal increase of RCTs with ITT was observed. Application of ITT methods yields unbiased and valid estimates not compromising the balance between the groups achieved by randomization [22]. A study that evaluated ITT principles in superiority trials of structural
outcomes in adult rheumatic diseases between 1994 and 2003 also found that most of the RCTs employed per-protocol analysis [14]. They reported that about 28.6% of the studies had >20% missing data. The method of handling missing data was reported in 23.5% of the studies and the most prevalent method was the last observation carried forward approach [14]. In our study, most of the RCTs had <20% dropout rate and there was no significant increase in the dropout rates over time. However, in our study, only five RCTs reported the method of handling missing data, four of which used the last observation carried forward approach and one used sensitivity analysis.

The main objective of our study was to evaluate the quality of
RCTs in JIA, which was poor for most of the selected indicators.
However, some of the observed characteristics of the studies
highlighted the difficulties in conducting RCTs in this population.
We found that the sample size was ≤50 in more than half of the
included parallel RCTs. Some of the reviewed RCTs discussed explicitly the difficulties related to patient accrual. One of the
studies enrolled only 25 patients over a 3-yr period from seven
centres in the USA and Canada. Another study could not reach

<table>
<thead>
<tr>
<th>Quality indicators</th>
<th>Overall</th>
<th>1976–85 (n = 11)</th>
<th>1986–95 (n = 17)</th>
<th>1996–2006 (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate generation of allocation sequence (%)</td>
<td>21 0 18 33(^a)</td>
<td>21 10 18 33(^a)</td>
<td>21 10 18 33(^a)</td>
<td>21 10 18 33(^a)</td>
</tr>
<tr>
<td>Adequate allocation concealment (%)</td>
<td>37 9 12 67(^d)</td>
<td>37 9 12 67(^d)</td>
<td>37 9 12 67(^d)</td>
<td>37 9 12 67(^d)</td>
</tr>
<tr>
<td>Adequate masking(^a) (%)</td>
<td>73 82 71 71</td>
<td>73 82 71 71</td>
<td>73 82 71 71</td>
<td>73 82 71 71</td>
</tr>
<tr>
<td>ITT(^b) (%)</td>
<td>37 18 18 58(^d)</td>
<td>37 18 18 58(^d)</td>
<td>37 18 18 58(^d)</td>
<td>37 18 18 58(^d)</td>
</tr>
<tr>
<td>Dropout rate ≤ 20% (%)</td>
<td>67 55 71 67</td>
<td>67 55 71 67</td>
<td>67 55 71 67</td>
<td>67 55 71 67</td>
</tr>
<tr>
<td>Clearly stated primary outcome (%)</td>
<td>50 36 23 75(^d)</td>
<td>50 36 23 75(^d)</td>
<td>50 36 23 75(^d)</td>
<td>50 36 23 75(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Adequate masking was compared with inadequate and unclear masking. \(^b\) Full or modified ITT was compared with per-protocol and unclear analysis. \(^d\) \(P < 0.05\) between the second and the third decades.
the needed sample size of 15 patients in the planned 18 months and was stopped early. Almost half of the studies failed to show a significant difference between the compared treatments—in some cases likely due to small sample sizes and low power. The results were neither associated with the levels of quality indicators nor with the source of funding. Lack of objective outcomes is another difficulty in this population. Although the ACR Pediatric 30 is a validated response measurement, it is a composite outcome and the clinical interpretation of the results can be challenging. Moreover, depending on the compared treatment methods (e.g., medication, massage therapy, behavioural interventions, surgery) the optimal outcome measurement may not be the ACR Pediatric 30. About half of the studies were either multicentre or multinational as a way to facilitate patient accrual. Alternative designs were also employed to make the studies more acceptable and more powerful. One-fifth of the RCTs in JIA used non-traditional designs such as cross-over and randomized withdrawal designs.

Study quality is relevant to the interpretation of study results. Several studies showed that the low quality studies are more likely to yield biased results [23, 24]. In our study, we did not see significant associations between the quality indicators and the study results. However, this type of conclusion depends also on the number of included studies (n = 52), which is relatively small compared with previous studies.

One of the limitations of our study was that only English language and full-text articles were included. We believe that this will not likely bias the results of the study because when the disease is rare and it is not easy to conduct an RCT, there should likely be more desire to report the results in English language journals. Moreover, the inclusion or exclusion of non-English language articles is felt by methodologists to be more of an issue when the systematic review is focused on treatment effectiveness rather than study quality [25]. Another limitation might be the reporting quality of the studies. It is possible that reporting quality is not always a good measure of the actual methodological quality of a study [26]. For example, we accepted masking as adequate if the authors named or described it as such. We categorized allocation concealment or method of random number generation as unclear if no information was available from the articles. This deficiency can be related to other factors related to reporting (e.g. journal word count restrictions) rather than the methodological quality of RCTs. In contrast, some of the components we have measured were directly related to methodological quality (such as ITT and dropout rate). However, the methodological and reporting quality of the studies are usually thought to be highly related [27]. Due to the constraints of feasibility we did not evaluate the methodological quality of RCTs by JIA subtype. Future investigators should be aware that the response to the treatment and the choice of the appropriate outcome can differ between the different subtypes. This is a further complicating issue for RCTs for this disease.

In summary, the overall quality of RCTs in JIA has been poor and there have been very few RCTs. As a result, there is little high-quality evidence for many current practices in JIA. There are positive changes in some of the indicators over time but more efforts should be made for further improvements of the design, conduct and reporting of the studies. In particular, studies should report the method of random number generation and allocation concealment, should make studies double masked whenever possible, conduct ITT analysis and ensure complete follow-up as far as possible. Considering the current difficulties in conducting RCTs in this population—and the likelihood that the studies will continue to be relatively few—both patients and physicians will benefit if more powerful and acceptable study designs will be used in the future. Perhaps this can be achieved by the development and testing of new designs for intervention trials for rare diseases.

### Acknowledgements
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**Disclosure statement:** The authors have declared no conflicts of interest.

### Supplementary data
Supplementary data are available at *Rheumatology* Online.

### References

Clinical Vignette

Aortic angiosarcoma mimicking large-vessel vasculitis: a diagnostic dilemma

A 55-yr-old lady presented with myalgia, arthralgia and claudicant thigh pain. Examination showed mildly reduced global power and reduced distal leg pulses. Investigations revealed grossly elevated inflammatory markers. Further detailed investigations were normal except abdominal CT and angiogram that showed almost complete occlusion of the distal aorta supporting a working diagnosis of a large-vessel vasculitis (LVV).

Sequential treatment with prednisolone, infusions of cyclophosphamide and methylprednisolone and insertion of an aortic stent resulted in only minor symptomatic improvement and continued elevation in blood inflammatory markers. Despite infliximab for a working diagnosis of treatment-resistant LVV, new symptoms of left tibial pain and a raised serpiginous rash occurred. Left tibial imaging revealed a destructive osteolytic lesion. Skin and bone biopsies revealed a high-grade multi-focal epithelioid angiosarcoma.

This lady died despite chemotherapy and palliative radiotherapy. A post-mortem confirmed the diagnosis of primary aortic angiosarcoma (PAA).

PAA is extremely rare (30 cases reported in the literature). It has a very poor prognosis and most commonly originates in the descending thoracic or abdominal aorta [1]. This case highlights the diverse presentations of malignancies and the high index of suspicion required with cases of vasculitis that are poorly responsive to conventional treatments.

Disclosure statement: The authors have declared no conflicts of interest.

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